The Journal of Allergy

VOL. 9 MARCH, 1938 NO. 3

Original Articles

EVIDENCE OF GROUP SPECIFIC AND SPECIES SPECIFIC SENSITIZATION TO POLLEN*

GLENN D. GRUBB, M.D., AND WARREN T. VAUGHAN, M.D.
RICHMOND, VA.

ALTHOUGH the number of species of weeds and grasses which might cause hay fever or asthma is enormous, fortunately only a few conform to all of Thommen's five postulates and need, therefore, be considered as of importance in endemic or epidemic pollinosis. These postulates are: (1) that the pollen must contain an excitant of hay fever; (2) that it must be wind-borne; (3) that it must be produced in sufficiently large quantities; (4) that it be sufficiently buoyant to be carried long distances; (5) that the plants producing the pollen must be widely and abundantly distributed. Since most weed and grass pollens fail in one or more of these postulates, it develops that not more than fifty are of more than local significance.

EVIDENCE OF GROUP SPECIFICITY

As pollen studies progressed it became apparent that there is a clearly recognizable tendency toward crossed reactions among pollens from plants belonging to the same family or genus. Scheppegrell[1] (1923), testing patients allergic to grass with over 100 varieties of grass pollen observed positive reactions to all, as contrasted with simultaneous negative reactions to other pollens. He interpreted this as a family, group, or crossed reaction. He observed clearly recognizable variations in the intensity of the reaction to different grass pollens.

Thommen[2] (1931) reached similar conclusions in a study of 30 patients tested with the pollens of 81 species, representing 50 genera. Among Americans atopic to grass, he observed positive reactions to the pollen of a grass indigenous to Spain to which they had never been exposed.

*From the Vaughan-Graham Clinic.

Cooke and Vander Veer[3] found that in New York City grass sensitization was almost invariably associated with allergy to timothy. They concluded that there is a crossed reaction among the grasses and that timothy desensitization adequately protects against other grasses. Freeman,[4] Goodale,[5] and others agree with these observations. Chobot[6] has shown that timothy pollen extract desensitizes against Bermuda grass and vice versa.

Similar observations have been made with the compositae. Walker[7] (1921) found that from 21 to 50 per cent of his ragweed-sensitive cases gave simultaneously positive reactions to goldenrod, daisy, golden glow, and sunflower. Vaughan and Crockett[8] found that in Virginia one out of every 3 patients with ragweed allergy was also allergic to goldenrod.

Cooke, Vander Veer, and Spain,[9] Aaron Brown,[10] and Spain and Hopkins[11] on direct skin testing found simultaneous positive reactions to giant and short ragweed, with no recognizable quantitative difference.

Evidence indicating the biologic identity of the reagens of giant and short ragweed has been presented in passive transfer experiments by Coca and Grove,[12] Stull, Cooke, and Chobot,[13] while Walzer and Grove[14] reached similar conclusions using the Dale uterine strip technique.

Bernton[15] reported an experience analogous to that of Thommen with an exotic pollen. He found a positive cutaneous reaction to tithona, a South American composite, in a ragweed allergic patient.

Sellers and Adamson[16] concluded from passive transfer studies that the antigenic properties of the amaranths are identical and that those of the chenopods are very similar but not identical. They concluded that desensitization with any member of the first group will control symptoms due to other members of the two classes of plants.

The accumulated evidence just reviewed appeared to justify the conclusion that adequate hyposensitization could be accomplished clinically by the use of but one member of any biologic group to which an individual is allergic. This materially simplifies the problem of the commercial preparation of pollen extracts and, as we shall see, probably accounts in part for the not infrequently observed failure of commercial extracts to achieve desired results.

EVIDENCE OF SPECIES SPECIFICITY

We have stated above that evidence of crossed pollen reaction was usually observed, but that a quantitative variation was often recognized. Watson and Kibler[17] (1922) found that a large number of their patients, allergic to Bermuda grass, did not show positive skin reactions to timothy and questioned the exclusive use of the timothy pollen extract in treatment. Lamson and Miller,[18] also Piness and Miller[19] reached similar conclusions. Coca and Grove[12] found that timothy desensitized areas passively sensitized to orchard grass but that orchard

grass did not completely desensitize against timothy. They concluded that some of the atopens of timothy are not present in orchard grass.

Rackemann and Wagner[20] working with timothy, orchard grass, and redtop have reported conclusions which would indicate that timothy is not a universal desensitizer for the grass family in the New England States. They state, "Crossed reactions between different grasses and between different trees are by no means unusual. Treatment of a passively sensitized site with either timothy, orchard grass, or redtop results in most instances in a simultaneous desensitization with the other two grasses, but the important fact is that no one of the three grasses always and invariably produces a desensitization to the other two. Observation of patients in the Clinic indicates that whereas most of our patients with early hay fever show positive skin reactions to all of the grass pollens at the same time and in about the same degree, there are occasional instances of single sensitivity and in other instances reactions to only two of several grasses. Furthermore, our results of treatment with a single grass pollen extract have not been as satisfactory as the results in other cases in which at least two pollen extracts were used."

Bernton,[21] also Rappaport and Johnson[22] found differences in the intensity of skin reactions to extracts of giant and short ragweed. This has been our own experience. Occasionally we have seen positive reaction to the short ragweed with a completely negative one to giant, confirmed on retesting and vice versa.

Moore, Cromwell, and Moore,[23] Armstrong and Harrison,[24] Cromwell and Moore,[25] and Cooke, Stull, Hebald, and Barnard,[26] using various methods of study such as passive transfer, reagin exhaustion, rabbit antiragweed serum, the trypan blue reaction in sensitized rabbits, reagin neutralization, and therapeutic studies, all reached the conclusion that the allergens of giant and short ragweed are not identical in spite of the commonly observed crossed positive skin reaction.

The evidence would indicate that although biologically related pollens show common antigenic activities, these are not completely identical for all pollens, each pollen possessing a reactive capacity of its own which may differ from that of other members of the same family. We may speak of group positive reactions and species positive reactions.

As a matter of fact this is what one would anticipate in view of past similar observations with other antigens. Wells,[27] also Hektoen and Cole[27] observed five antigenic components of hen's egg some of which were identical with those of duck egg, others not. It is well known that the lactalbumin fraction of milk tends to be species specific while the casein fraction is usually antigenically similar for all milks. Wells found an identical antigen in wheat and rye, a closely related one in barley, and at the same time species specific antigens in all three. Vaughan,[28] Baldwin,[29] and Withers[30] have observed group sensitiza-

tions among the common foods and, at other times, individual sensitization within the members of the groups. Talbott,[31] Freeman,[32] and Walzer and Bowman[33] have demonstrated similar group and individual reactivities among horse, donkey, and zebra allergens. A similar situation has been shown to exist in the lower forms of life such as amebae and bacteria.[34] Among the bacteria group reactions in the typhoid-paratyphoid group, and the specific carbohydrate and protein reactions in the pneumococcus group are familiar examples.

CLINICAL APPLICATION

For the last fifteen years it has been the custom in this Clinic to test with several different species of the weed and grass family rather than with one or a few representative members. In 1931 Vaughan[35] reported on the relative frequency of positive skin reactions (Table I). He found

TABLE I

POSITIVE SKIN REACTIONS TO POLLEN EXTRACTS (VAUGHAN, 1931)

PLANT	FREQUENCY	PLANT	FREQUENCY
Gramineae		*Amaranthaceae*	
Timothy	26	Redroot Pigweed	4
June Grass	20	Spiny Amaranth	6
Orchard Grass	20		
Redtop	28	*Compositae*	
Sweet Vernal Grass	16	Ragweed, Short	100
Bermuda Grass	18	Ragweed, Giant	94
Brome Grass	24	Marsh Elder	12
Wire Grass	28	Common Mugwort	14
Barnyard	6	Sunflower	32
Crab Grass	8	Daisy	24
Johnson Grass	22	Goldenrod	30
Rye	2	Dandelion	22
Wheat	8	Dahlia	2
Corn	16		
		Miscellaneous	
Chenopodiaceae		Rose	18
Lamb's-quarters	6	English Plantain	22
Russian Thistle	12	Dock	4
Sugar Beet	6		

Using Short Ragweed as 100 per cent, 94 will be positive to Giant Ragweed, 26 to Timothy, etc.

that while there was a definite tendency toward group reaction, this was not constant since some pollens reacted positively much more frequently than other members of the same family. Among the grasses, those which are generally recognized as causing pollinosis most frequently gave the most frequent positive reactions, but even here there was distinct variation. Grasses which are not widely distributed through the southeastern states and whose pollen is therefore not abundant, and pollen from plants which shed little pollen, such as wheat, rye, crab grass, and barnyard grass produce few positive skin reactions. Similar observations were made among the composites, the chenopods, and the amaranths.

It has also been our custom to desensitize whenever indicated, with several species of the same family, based upon the information gained from testing.

The existence of family or genus specific allergens is now quite generally accepted. The purposes of the present communication are as follows: (1) to present evidence of species specificity within the group; (2) to present evidence of the occasional importance of the recognition of species specificity in therapy; (3) to study evidence of sensitization to pollens to which the individual has presumably not been intensively exposed; (4) to search for evidence of crossed sensitization to different parts of the same plant as exemplified in positive reactions to the pollen and food of single plants.

This is primarily a clinical study and represents the practical application of the results of the experimental investigations of others cited above. No passive transfer studies were made. Our experience has been that in the southeastern states if a person is sufficiently allergic to a pollen for the latter to cause symptoms, he will react by scratch test with 2 per cent extract. Endermal testing and conjunctival tests were, therefore, used only in cases where a doubt remained after scratch testing. Since the two latter procedures were not employed in every case, the present study is based only upon dermal skin testing. The writers are fully cognizant of the disadvantage of dermal testing, the possibility of false negative reaction. However, as stated, we find that the information obtained from scratch testing with pollens corresponds remarkably well with the patient's symptom sequence, and the results of treatment based on scratch tests are adequate. We, therefore, feel that in this instance conclusions based upon the findings are acceptable. We do not find this to be the case with other allergens, where endermal testing is also found requisite. Furthermore, the volume of material reviewed minimizes the factor of possible occasional false negative reactions. The technique of testing has been a constant factor in each instance, and where a doubt has existed, scratch tests have often been repeated.

The study comprises a review of the last 300 cases of pollinosis, each of which was tested routinely with each of the pollen extracts listed on Tables II to V.

EVIDENCE OF SPECIES SPECIFICITY

Two hundred and eighteen of the 300 cases studied reacted positively to one or more members of the grass family (Table II). There was no one grass which caused positive reactions in all patients allergic to grass. Redtop did so most frequently, being positive in 65.6 per cent of them. It is obvious from the first column (totals) of Table II that no single grass extract can be used as a universal testing medium. It is of in-

terest that in this series, as in Vaughan's series of 1931 (Table I), redtop more nearly approached this than any other grass, much more so than timothy.

That this is probably more than coincidental is indicated by our experience with conjunctival tests. For some time it had been our custom, with individuals whose history indicated grass allergy but who failed to give positive skin reactions, to attempt to establish evidence of grass sensitization by conjunctival test with timothy as a representative of the family. In some cases this procedure established the existence of grass allergy, in others it did not. After recognizing the apparently higher frequency of positive redtop reactions we changed the ophthalmic program to preliminary testing with timothy, followed by redtop testing if the former was negative. In this way we found that a presumptive patient allergic to grass and negative by conjunctival test to dry timothy pollen would often react positively with redtop. We found that redtop was a better family representative for this test than timothy.

This does not necessarily imply that the same would be true in New York or elsewhere where the relative concentration of grass pollens in the air is different. As has been noted in the discussion of Table I there is a tendency toward fewer reactions to the pollen of a grass to which the individual is less frequently exposed. However, until it has been shown that this is not true in other sections of the country, the evidence in Table II strongly indicates that redtop is the most promising single testing agent of those grasses used. The table, reading across (not down), indicates the frequency with which a person reacting to a given grass also reacted to others. It will be seen that of 97 individuals positive to Johnson grass, 82.3 per cent were also allergic to redtop. Of 90 positive to crab grass, 84.4 per cent were also positive to redtop. The redtop vertical column, ranging from 81.5 per cent to 87.6 per cent is much higher than any other vertical column. Given a positive reaction to any single pollen in the left hand column, the probability of observing a simultaneous positive reaction to redtop is decidedly greater than that of any other pollen studied.

The percentage probability of any grass listed across the top of Table II, reacting positively in the presence of positive reactions to any grass in the left hand column is indicated across the bottom of the table. It will be seen that redtop leads easily, followed successively by sweet vernal grass, orchard grass, June grass, and timothy.

Approximately 25 per cent of the 218 patients allergic to grass reacted to all 10 of the grasses used in testing. Thirty-seven or 17 per cent reacted to but 1 pollen (figures in parenthesis in Table II). The remainder cross reacted with from 1 to 8 other grasses.

TABLE II

Gramineae 218 POSITIVE CASES (72.6 PER CENT)

	TOTAL	PER CENT	JOHNSON GRASS		CRAB GRASS		REDTOP		SWEET VERNAL GRASS		TIMOTHY		BERMUDA GRASS		ORCHARD GRASS		VELVET GRASS		JUNE GRASS		BROME GRASS	
			NO.	PER CENT	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT
Johnson Grass *Holcus halepensis*	97	44.5	(3)		64	65.9	80	82.3	69	71.0	63	64.9	48	49.2	64	65.9	39	40.2	64	65.9	56	57.7
Crab Grass *Panicum dichotomiflorum*	90	41.3	64	71.1	(5)		76	84.4	63	70.0	57	63.3	45	50.0	55	61.1	39	43.3	59	65.5	55	61.1
Redtop *Agrostis alba*	143	65.6	80	55.2	76	53.1	(5)		97	67.8	82	57.3	62	43.3	90	62.9	50	34.9	93	65.0	74	51.7
Sweet Vernal *Anthoxanthum odoratum*	119	54.6	69	57.1	63	54.6	97	81.5	(4)		75	63.0	54	45.3	77	64.7	50	42.0	77	64.7	63	54.6
Timothy *Phleum pratense*	99	45.4	63	63.6	57	57.5	82	81.8	75	75.7	(7)		48	48.3	69	69.6	41	41.4	69	69.6	58	58.4
Bermuda *Capriola dactylon*	76	35.1	48	63.1	45	59.2	62	81.8	54	71.0	48	63.1	(4)		55	72.3	29	38.1	50	65.7	46	60.5
Orchard Grass *Dactylis glomerata*	105	48.1	64	60.9	55	52.3	90	85.7	77	73.3	69	65.7	55	52.3	(2)		45	43.3	78	74.2	67	63.8
Velvet Grass *Nothoholcus lanatus*	57	26.1	39	68.4	39	68.4	50	87.6	50	87.6	41	71.9	29	50.8	45	78.9	(1)		41	71.9	33	57.8
June Grass *Poa pratensis*	112	51.4	64	57.1	59	52.6	93	83.0	77	60.7	69	61.6	50	44.6	78	69.6	41	36.6	(3)		60	53.1
Brome Grass *Bromus secalinus*	86	39.4	56	65.1	55	63.9	74	86.0	63	73.2	58	67.4	46	53.4	67	77.8	33	38.1	60	69.7	(3)	
Average				62.4		58.6		83.8		72.3		64.2		48.6		69.2		39.8		68.0		57.6

Total cases studied 300.

The 37 single positive grass reactions are of especial interest. They were all clear-cut positive reactions. The question of false negative reactions to the other grasses can scarcely be raised, since each single positive had 9 negative controls. This observation is of real importance in the present discussion, in as much as it indicates that in 17 per cent of the 218 cases, sensitization was completely species specific and there was no evidence of group reaction. Furthermore, this condition existed with every grass used for testing and is therefore probably true for all hay fever grasses. Obviously, therefore, no one grass may be used as a representative of the family for routine testing. If we were to take redtop as the most promising single grass for testing we would find that approximately 15 per cent of grass allergics would react to some other single grass, with no multiple reactions. Furthermore, of the single and multiple reacting allergics, only approximately 66 per cent will react to redtop.

If redtop alone were used for testing, one-third of the cases of grass sensitization would be missed. If multiple diagnostic testing were done as indicated in Table II and redtop alone were used in treatment, it would be reasonable to assume that no benefit would be obtained in the 15 per cent that were allergic only to species specific allergens (not including redtop). The degree of benefit with the remainder would depend upon the relative proportion of group specific and species specific allergens.

Similar conclusions may be drawn from a study of the *compositae* (Table III). Of the 300 patients with pollen allergy, 255 or 85 per cent reacted to one or more members of the group. Two hundred and thirty or 92.2 per cent of the 255 reacted to short ragweed. We see from the percentage figures across the base of the chart that short ragweed would give greatest promise of being a universal test substance (90 per cent), followed by giant ragweed. The remainder of this group show no promise at all.

Also, in this group it should be noted that with the exception of sunflower every member tested showed one or more species specific reactions with no evidence of crossed reaction at all. Short ragweed showed this most frequently although giant ragweed, goldenrod, and daisy showed it in several patients. Here again one must conclude that for fullest information individual testing should be performed.

It should be borne in mind that the allergens listed in Table III are for the greater part not as closely related as are the grasses previously discussed. While they are grouped as *compositae,* dandelion is a member of the *chicoriacae;* the ragweeds and marsh elder of the *ambrosiacae;* while the remainder all belong to different tribes of the tremendous *compositae* family, except for goldenrod and daisy which are members of the same tribe.

TABLE III

Compositae 255 POSITIVE CASES (85 PER CENT)

	TOTAL	PER CENT	SHORT RAGWEED		GIANT RAGWEED		GOLDENROD		DAISY		DANDELION		MARSH ELDER		SUNFLOWER		MUGWORT	
			NO.	PER CENT	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT
Short Ragweed *Ambrosia artemisiafolia*	230	90.2	(9)		180	78.2	103	44.7	71	30.9	52	22.6	50	21.7	55	23.9	39	16.9
Short Ragweed *Ambrosia elatior*	192	71.3	180	94.1	(5)		83	43.2	58	30.2	48	25.0	48	25.0	53	27.6	36	18.2
Goldenrod *Solidago*	110	39.2	103	93.6	83	75.4	(5)		45	40.9	31	28.1	32	29.1	37	33.6	30	27.2
Daisy *Chrysanthemum leucanthemum*	79	30.9	71	89.8	58	73.3	45	56.9	(6)		22	27.8	22	27.8	33	41.7	20	25.3
Dandelion *Leontodon taraxacum*	59	23.1	52	88.1	48	81.3	31	50.8	22	37.3	(1)		22	37.3	29	49.1	24	40.6
Marsh Elder *Iva frutescens*	58	22.7	50	85.8	48	82.7	32	55.2	22	37.9	22	37.9	(3)		22	37.9	25	43.1
Sunflower *Helianthus annuus*	58	22.7	55	94.8	53	91.4	37	63.7	33	56.9	29	50.0	22	37.9	(0)		21	36.2
Common Mugwort *Artemisia vulgaris*	45	17.6	39	86.6	36	80.0	30	66.6	20	44.4	24	53.3	25	55.5	21	46.6	(1)	
Average				90.4		80.3		54.4		39.8		34.9		33.5		37.2		29.6

Parenthesis=single reaction.

THE IMPORTANCE OF RECOGNITION OF SPECIES SPECIFICITY IN THERAPY

This has been amply brought out in the preceding section. Since in this Clinic, grass hyposensitization has always been carried out with multiple antigens, it is difficult to cite specific examples showing the value of species specific therapy. This is more easily done with the *compositae*. Vaughan and Crockett have emphasized that one out of every three ragweed allergy patients is also sensitive to goldenrod. In the present study, nearly half of those reacting to ragweed reacted also to goldenrod. As a rule we have found that ragweed desensitization is all that was necessary for relief in these ragweed-goldenrod allergic individuals. However, in a small number, adequate relief has not been obtained from preseasonal treatment. When this has been the case, coseasonal goldenrod therapy was added to the program, with resultant relief. This was especially so with persons living in the country or at the edge of town, where they were rather closely exposed to goldenrod pollen. Presumably this small group was species allergic to goldenrod.

We have recently treated two cases of ragweed allergy who also gave strongly positive reactions to dandelion. During the dandelion season one of these was receiving perennial ragweed desensitization, the other preseasonal treatment. They both developed hay fever in May. Three coseasonal injections of dandelion extract in high dilution (1:5,000) promptly gave complete relief. Here was one case that had been adequately desensitized against ragweed and was receiving perennial treatment, which did not protect him against the species specificity to dandelion. The other case was receiving early preseasonal ragweed treatment which did not protect against dandelion. However, similar dosage of dandelion extract promptly relieved.

We have had similar experience with dahlia. A woman who lived next door to a dahlia nursery was allergic to ragweed. She had had preseasonal ragweed treatment several times without adequate relief. We found her positive to dandelion and dahlia. Combined preseasonal treatment with both extracts in 1937 gave her the first relief that she had experienced.

SENSITIZATION TO POLLENS TO WHICH THE INDIVIDUAL HAS HAD LITTLE OR NO EXPOSURE

Owing to the wide distribution of at least some members of any botanical family, it is difficult to select for this purpose a group of pollens which produce hay fever which (1) are entirely lacking in a given territory and (2) have no nearly related relatives in the territory. Instead of endeavoring to comply with these specifications we have tested the 300 patients routinely with the pollens of those plants which are of major importance elsewhere but which, although they

TABLE IV

Chenopodiales

Amaranthaceae 47 CASES—15.6 PER CENT *Chenopodiaceae* 126 CASES—42 PER CENT

	TOTAL	PER CENT	SPINY AMARANTH		REDROOT PIGWEED		WESTERN WATER HEMP		RUSSIAN THISTLE		SUGAR BEET		LAMB'S-QUARTERS	
			NO.	PER CENT	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT
Amaranthaceae														
Spiny Amaranth *Amaranthus spinosus*	24	49.8	(5)	20.8	3	12.5	3	12.5	13	54.1	8	33.3	1	4.2
Redroot Pigweed *Amaranthus retroflexus*	21	44.7	3	14.3	(10)	47.6	0	0	4	19.0	7	33.3	4	19.0
Western Water Hemp *Acnida tamariscina*	8	17.1	3	37.5	0	0	(0)	0	5	62.5	3	37.5	3	37.5
Chenopodiaceae														
Russian Thistle *Salsola pestifer*	70	55.5	13	18.6	4	5.7	5	7.1	(28)	40.0	27	38.6	11	15.7
Sugar Beet *Beta vulgaris*	68	54.0	8	11.7	7	10.3	3	4.4	27	39.7	(29)	42.6	12	17.3
Lamb's-quarters *Chenopodium album*	26	20.6	1	3.8	4	15.4	3	11.5	11	43.1	12	46.2	(8)	30.7

Total cases studied 300.

may be present along the southeastern seaboard, are of negligible importance in causing hay fever. This comprises representatives of the pigweed and goosefoot family. Although spiny amaranth, redroot pigweed, and lamb's-quarters are found in this territory and although positive reactions were observed to all of the plants listed in Table IV, we have never found it necessary to give treatment except with lamb's-quarters extract. With the exception of the latter, these plants are negligible in Virginia and the southeastern seaboard.

While a few of the patients reacting positively may have been temporarily in the west we feel that it is safe to assume that the majority have not been exposed to these pollens in sufficient concentration or for a long enough period to have been expected to develop sensitization.

Scheppegrell[36] (1917) grouped the chenopods and the amaranths into one family as far as hay fever was concerned and concluded that a pollen extract of any member of the group would desensitize against other members. Sellers and Adamson concluded from passive transfer studies that the antigenic properties of the amaranths are identical, that those of the chenopods are very similar but not identical to the former.

They studied spiny amaranth, redroot pigweed, Palmer's amaranth, western water hemp, Russian thistle, and lamb's-quarters all of which possess pollens which are microscopically very similar. They found that reaction to one member of the *chenopodiales* (amaranths and chenopods) was accompanied, with few exceptions, by reactions to all other members of the group. By passive transfer experiments they concluded that all atopens of the six species studied were contained in the pollens of *Amaranthus spinosa, Amaranthus palmeri, Amaranthus retroflexus* and *Acnida tamariscina,* but that all of the atopens were not contained in the pollens of *Salsola pestifer* or *Chenopodium album.* They suggested that treatment with amaranth pollen should control allergy to all six species studied.

In our own study we were surprised at the high frequency of reactions to members of this group. Forty-two per cent of the 300 patients gave reactions to chenopods. Of these, approximately 55 per cent reacted to Russian thistle and sugar beet, pollens to which they were scarcely exposed in sufficient quantity, theoretically, to produce sensitization. Sugar beet pollen is anemophilous and causes pollinosis among those who cultivate it. They were exposed to higher concentration of lamb's-quarters, but sensitization to this was decidedly less than that to the former. Fifteen per cent of the 300 reacted to amaranths. In this group they reacted more frequently to those to which they had theoretically higher exposure. With the exception of western water hemp, the total number of which is too small to be significant, every member gave species specific reactions as well as what appeared to be family specific reactions. Indeed, the frequency of

species reaction was much higher than with the grasses and *compositae* and would suggest that, contrary to the conclusions of Sellers and Adamson, for best results one should test with each individual member as well as with any grouping thereof.

The question arises as to why 42 per cent of allergic individuals react positively by skin test to pollens to which they theoretically had insufficient exposure to develop sensitization, pollens which do not cause symptoms in spite of the positive skin reactions. The answer is not readily forthcoming, although the fact remains. Unrecognized previous exposure; group reaction due to sensitization to some related plant; hereditary predisposition to sensitization to a specific allergen as suggested by Coca, are possibilities. Spread from a neighboring positive skin reaction is improbable with the technique employed. One may speak of a false positive skin reaction, but this is a designation, not an explanation, and in itself requires explaining.

TABLE V

POSITIVE SKIN REACTIONS WITH FOODS AND CORRESPONDING POLLENS—300 CASES

LATIN NAME	COMMON NAME	FOOD		POLLEN		POLLEN AND FOOD	
		NO. CASES	PER CENT	NO. CASES	PER CENT	NO. CASES	PER CENT
Triticum sativum	Wheat	104	34.6	48	16.0	24	50.0
Zea mays	Corn	106	35.3	41	13.6	27	66.0
Chenopodiaceae	Beet Group	87	25.6	68	22.6	39	57.4

SENSITIZATION TO FOOD AND POLLEN FROM THE SAME PLANT

Farmer[37] found that "although a close immunologic relationship between the pollens of different grasses may be assumed, it has been shown—that there is no immunologic relationship between the pollens and the seeds of the same plant, in spite of their close biological relationship." Differences have been observed in the intensity of the skin reaction to pollens, leaves, and roots of the same plant. Organ specificity among the animal allergens is well known. This involves such tissues as the crystalline lens, the integument, serum glandular secretions, and probably also certain of the parenchymatous tissues themselves.

It will be seen from Table V that among the 300 cases studied, 48 reacted to wheat pollen, 104 to wheat food. Food tests were performed both by scratch and intracutaneous methods. One-half of those who reacted to wheat pollen also reacted to the food. Slightly under one-fourth of those reacting to wheat as a food also reacted to wheat pollen. The table indicates that with the three foods tested, wheat, corn, and beets, from one-half to two-thirds of those reacting to the pollen also reacted to the food. From 23 to 45 per cent of those allergic to the food also reacted to the pollen from that plant. It

should be borne in mind that these are cases of pollinosis and this latter figure would not necessarily hold for a food-allergic patient with no respiratory symptoms.

MISCELLANEOUS REACTIONS

Additional pollens to which the 300 cases were routinely tested are indicated in Table VI. Table VII represents a combination of the 100 cases studied by Vaughan in 1931 and the 300 discussed in the present communication, and gives the relative frequency of sensitization to the various pollens studied, using short ragweed, the most frequently reactive pollen, as the unit for comparison.

TABLE VI

SKIN REACTIONS TO MISCELLANEOUS POLLENS—300 CASES

LATIN NAME	COMMON NAME	FREQUENCY	PER CENT
Plantago lanceolata	English Plantain	63	21.0
Rumex acetosella	Sheep Sorrel	56	18.6
Rosaceae spp.	Rose	46	15.3
Rumex crispus	Narrow Leaf Dock	30	10.0
Typha latifolia	Cat-tail	25	8.3

TABLE VII

COMBINED STATISTICS OF VAUGHAN, 1931, AND GRUBB AND VAUGHAN, 1937
400 CASES

PLANT	FREQUENCY	PLANT	FREQUENCY
Gramineae		*Amaranthaceae*	
Timothy	38	Redroot Pigweed	7
June Grass	40	Spiny Amaranth	9
Orchard Grass	38		
Redtop	52	*Compositae*	
Sweet Vernal Grass	41	Short Ragweed	100
Bermuda Grass	29	Giant Ragweed	87
Brome Grass	33	Marsh Elder	21
Crab Grass	29	Common Mugwort	18
Johnson Grass	36	Sunflower	25
Wheat	17	Daisy	31
Corn	17	Goldenrod	42
Velvet Grass	17	Dandelion	25
Chenopodiaceae		*Miscellaneous*	
Lamb's-quarters	10	Rose	19
Russian Thistle	26	English Plantain	28
Sugar Beet	22	Dock	10

Using Short Ragweed as 100 per cent, 87 were positive to Giant Ragweed, 38 to Timothy, etc.

CONCLUSIONS

Study of closely related pollens derived from the same botanical families shows evidence of the existence of group specific and species specific allergens. No single pollen studied in any of the groups, grasses, composites, amaranths, or chenopods, was found which could be considered representative of any entire group.

Among the grasses studied, redtop was found to cross react most frequently with other grasses, but the frequency was not sufficiently high to justify its use as a single pollen for the recognition of grass allergy. Short ragweed holds a similar place among the composites.

Because of the surprisingly high frequency of positive skin reactions to only one pollen of a group, the writers conclude that for best diagnostic and therapeutic results testing should be done with all individual pollens under suspicion.

When several pollens within a group react positively it is sometimes necessary to hyposensitize with more than one of the positive reactors. This may apply under certain circumstances even to entomophilous pollens.

In the series studied, a number of patients were found with positive skin reactions to pollens to which they had presumably not had sufficient exposure to develop sensitization. No final explanation is offered.

About half of those patients allergic to the pollen of food plants, wheat, corn and beet, were also allergic to the corresponding foods.

REFERENCES

1. Scheppegrell, W.: Immunological Classification of Common Hay Fever Plants and Trees, M. J. & Rec. **117**: 721, 1923.
2. Coca, A. F., Walzer, M., and Thommen, A. A.: Asthma and Hay Fever in Theory and Practice, Springfield, 1931, Charles C. Thomas.
3. Cooke, R. A., and Vander Veer, A., Jr.: Human Sensitization, J. Immunol. **1**: 201, 1916.
4. Freeman, J.: Further Observations of the Treatment of Hay Fever by Hypodermic Inoculation of Pollen Vaccine, Lancet **2**: 814, 1911.
5. Goodale, J. L.: Preliminary Notes on the Anaphylactic Skin Reactions Excited in Hay Fever Subjects by the Pollens of Various Species of Plants, Boston M. & S. J. **171**: 695, 1914.
6. Chobot, Robert: Studies in Specific Hypersensitiveness; Relationship of Atopens in the Pollens of Bermuda Grass (Condyon dactylon) and Timothy Grass (Phleum pratense), J. Immunol. **16**: 281, 1929.
7. Walker, I. C.: Frequent Causes and Treatment of Seasonal Hay Fever, Arch. Int. Med. **28**: 71, 1921.
8. Vaughan, Warren T., and Crockett, R. W.: Assay of Goldenrod as a Cause of Hay Fever, Ann. Int. Med. **6**: 789, 1932.
9. Quoted by Cooke, R. A., Stull, Arthur, Hebald, Selian, and Barnard, James H.: Clinical and Serologic Study of Relationship of Giant (Ambrosia trifida) and Low (Ambrosia artemisiaefolia) Ragweed Pollen, J. ALLERGY **6**: 311, 1935.
10. Brown, A.: Studies in Hypersensitiveness; Identity of Atopens of Pollens of High Ragweed and Low Ragweed, J. Immunol. **13**: 73, 1927.
11. Spain, W. C., and Hopkins, M.: On Identity of Atopens of High Ragweed and Low Ragweed Pollen, J. ALLERGY **1**: 209, 1930.
12. Coca, A. F., and Grove, E. F.: Studies in Hypersensitiveness, Study of the Atopic Reagins, J. Immunology **10**: 445, 1925.
13. Stull, A., Cooke, R. A., and Chobot, R.: Identity of Allergically Active Substance in Giant and Low Ragweed Pollen, J. ALLERGY **3**: 120, 1932.
14. Walzer, M., and Grove, E. F.: Studies in Specific Hypersensitiveness; Antigens, Comparative Study of Antigenic Properties of Pollens, Egg-White, and Glue, in Guinea Pigs, as Determined by Intravenous and Dale Methods of Testing in Anaphylaxis, J. Immunology **10**: 483, 1925.
15. Bernton, Harry S.: Treatment of Seasonal Hay Fever and Some Possible Causes of Failure, J. A. M. A. **80**: 1301, 1932.
16. Sellers, Earle D., and Adamson, W. B.: Study of the Apparent Atopic Similarity of Certain Chenopodiales Pollens, J. ALLERGY **3**: 166, 1932.
17. Watson, S. H., and Kibler, C. S.: Etiology of Hay Fever in Arizona and Southwest, J. A. M. A. **78**: 719, 1922.

18. Lamson, R. W., and Miller, H.: Pollen Allergy; Genesis of Skin Hypersensitiveness in Man, Arch. Int. Med. **40**: 618, 1927.
19. Piness, G., and Miller, H.: Specificity of Pollen Allergens, J. ALLERGY **1**: 483, 1930.
20. Rackemann, F. M., and Wagner, H. C.: The Desensitization of Skin Sites Passively Sensitized With Serum of Patients With Hay Fever. Crossed Reactions of Different Pollens. The Variations in the Recipient, J. ALLERGY **7**: 319, 1936.
21. Bernton, H. S.: Immunologic Observations in Autumnal Hay Fever; With Special Reference to Treatment, J. A. M. A. **82**: 1434, 1924.
22. Rappaport, B. A., and Johnson, C. A.: Proc. Soc. Exper. Biol. & Med. **26**: 771, 1929.
23. Moore, M. B., Cromwell, H. W., and Moore, E. E.: Studies on Pollen and Pollen Extracts; Skin Reactions to Pollen Fractions, J. ALLERGY **2**: 85, 1931.
24. Armstrong, C., and Harrison, W. T.: Study of Ragweed Pollen Extracts for Use in Treatment of Ragweed Pollen Hypersensitiveness, Pub. Health Rep. **39**: 2422, 1924.
25. Cromwell, H. W., and Moore, M. B.: Studies on Pollen and Pollen Extracts, J. ALLERGY **4**: 347, 1933.
26. Cooke, R. A., Stull, A., Hebald, S., and Barnard, J. H.: Clinical and Serologic Study of the Relationship of Giant (Ambrosia trifida) and Low (Ambrosia artemisiaefolia) Ragweed Pollen, J. ALLERGY **6**: 311, 1935.
27. Wells, H. Gideon: The Chemical Aspects of Immunity, New York, 1925, The Chemical Catalogue Co.
28. Vaughan, Warren T.: Food Allergens. I. A Genetic Classification With Results of Group Testing, J. ALLERGY **1**: 385, 1930.
29. Baldwin, H. S., and Benedict, M. I.: Mutual Absorption Tests With Related Foods, J. ALLERGY **8**: 120, 1937.
30. Withers, O. R.: Food Allergens; a Statistical Analysis of Forty-Three Cases Relative to Genetic Classification of Foods, South. M. J. **30**: 918, 1937.
31. Talbott, F. B.: Long Island M. J. **11**: 245, 1917.
32. Freeman, J., From Hurst, A. F.: Lancet **1**: 1113, 1921.
33. Coca, A. F., Walzer, M., and Thommen, A. A.: Asthma and Hay Fever in Theory and Practice, Springfield, 1931, Charles C. Thomas.
34. Sherwood, Noble P.: Immunology, St. Louis, 1935, The C. V. Mosby Co.
35. Vaughan, Warren T.: Allergy and Applied Immunology, St. Louis, 1931, The C. V. Mosby Co.
36. Scheppegrell, W.: The Classification of Hay Fever Pollens From the Biological Standpoint, Boston M. & S. J. **177**: 42, 1917.
37. Farmer, Lawrence: On the Immunologic Relationship Between Grass Pollen and Seed, J. ALLERGY **8**: 338, 1937.

201 WEST FRANKLIN STREET

LIPIDS OF THE BLOOD PLASMA IN HAY FEVER AND ASTHMA*

II. The Unsaturated Fatty Acids in the Fat, Phospholipid, and Cholesterol Esters

Walter R. Bloor, Ph.D., Authur G. Blake, M.S., and Stearns S. Bullen, M.D.
Rochester, N. Y.

IN THE FIRST paper of this series, data were presented regarding the percentage of cholesterol and the percentage and iodine number of the total fatty acids of the blood plasma in a series of patients from the allergy clinic of this institution. When compared with values obtained from blood plasma of normal (non-sensitive) individuals, no definite difference in the amount or degree of unsaturation of the fatty acids could be noted.

It was thought, however, that even though the average degree of unsaturation (as shown by the iodine number) of the total fatty acids was the same in the normal as in the sensitive individuals, some differences might be present in the fractions of the total fatty acid present in the three main groups of fatty acid compounds in blood plasma, those of neutral fat, phospholipids, and cholesterol esters. Consequently a study was made of these separately.

PROCEDURE

Samples of blood (citrated) from patients in the allergy clinic were centrifuged and the plasma (about 10 c.c.) obtained; this was then added slowly to 200 c.c. of 3:1 alcohol-ether, heated to boiling, and filtered. The filtrate was evaporated on a water bath at less than 40° C. under diminished pressure.

The phospholipids were removed by the method of Bloor.[1] These were saponified and the fatty acids therefrom transferred to a 50 c.c. volumetric flask with petroleum ether. Aliquots were used to determine oxidatively the fatty acid content[2] and the iodine number of the same.[3]

The acetone solution from the separation of the phospholipids containing neutral fat, cholesterol, and cholesterol esters was evaporated on a water bath at less than 40° C. in a stream of CO_2. This residue was extracted into a 100 c.c. volumetric flask with petroleum ether and the combined extracts made to volume. Aliquots were taken for the oxidative determination of total fatty acids[2] and the digitonide determination of total and bound cholesterol.[4]

*From the Department of Biochemistry and the Department of Medicine, School of Medicine and Dentistry, University of Rochester, and the Medical Clinic of the Strong Memorial and Rochester Municipal Hospitals.

For the separation of the cholesterol esters from the neutral fat, a differential saponification of the mixture with castor bean lipase was used. This procedure was devised by Mr. F. E. Kelsey of this laboratory and is based on the fact that cholesterol esters are slowly, if at all, attacked by this lipase, while neutral fat is readily hydrolyzed by it. Five c.c. aliquots of the petroleum ether solution were placed in 1.5 by 15 cm. soft glass test tubes and evaporated in a stream of CO_2. Then, to each tube, 0.1 gm. of a castor bean lipase preparation made by hulling the beans, grinding, extracting thirty-six hours in a Soxhlet extractor with ethyl ether, and then grinding to pass an 80-mesh sieve was added, and 5 c.c. of an acetic acid sodium acetate buffer (pH 4.7). The saponification was then carried out as follows: The tubes were heated about 5 cm. from the top in a bunsen flame and drawn out to a fine capillary (about 1 to 2 mm. in diameter). They were allowed to cool, and 5 c.c. of petroleum ether introduced into each with the aid of a syringe. They were cooled further to about 5° C. by being placed in a salt-ice mixture and then sealed with a microburner. The tips were allowed to cool, and the tubes were shaken well to dissolve the lipids and then form an emulsion. They were then placed, for at least twelve hours, on a slowly revolving wheel (3 r. p. m.) from which they were removed occasionally and shaken to insure preservation of the emulsion.

The tubes were removed from the wheel and each treated in the following manner: The tip was broken into a 125 c.c. Erlenmeyer flask containing 50 c.c. of 95 per cent alcohol, and the contents allowed to run into the alcohol. Then the tube was broken cautiously so that all the pieces fell into the alcohol. The mixture was boiled and filtered, and the residue on the filter paper washed three times with 5 c.c. portions of ethyl ether. The alcohol-ether solution was made alkaline to congo red paper with 20 per cent sodium hydroxide and 50 c.c. of distilled water added to it. This solution was placed in a separatory funnel and extracted with 50 c.c. of petroleum ether. The petroleum ether fraction was washed with 25 c.c. of alkaline 50 per cent alcohol, the two alcohol fractions combined and extracted three times with 30 c.c. portions of petroleum ether. All these petroleum ether fractions, containing the cholesterol ester, were combined, evaporated to a small volume in a stream of CO_2, and transferred to a 25 c.c. volumetric flask with petroleum ether. Five cubic centimeter aliquots of this solution were saponified, the solution acidified and the fatty acids and cholesterol extracted with ether, the ether washed then evaporated, the residue taken up with alcohol, and the cholesterol removed with digitonin. After this, the fatty acids were separated, their content determined oxidatively[2] and the iodine number measured.[3]

For the examination of the neutral fat fatty acid, the alkaline alcohol fraction was made acid with 3:1 sulfuric acid and extracted four times with 25 c.c. portions of petroleum ether. These petroleum ether extracts

TABLE I

UNSATURATED FATTY ACIDS AND CHOLESTEROL IN PLASMA

	CHOLESTEROL		FATTY ACIDS					
	TOTAL	ESTER/ TOTAL	FROM NEUTRAL FAT		FROM PHOSPHOLIPID		FROM CHOLESTEROL ESTER	
			AMOUNT	I NO.	AMOUNT	I NO.	AMOUNT	I NO.
	mg. per cent	*per cent*	*mg. per cent*		*mg. per cent*		*mg. per cent*	
				Asthma				
	156	60.2	164	113	110	121	63.5	157
	213	63.8	297	100	143	121	91.8	175
	187	73.3	237	101	139	117	92.1	158
	206	71.8	189	109	159	123	107	161
	124	63.7	213	121	156	142	57.5	170
	176	72.7	187	103	125	113	91.7	159
	156	61.0	149	111	182	99	66.3	181
	218	62.6	175	97	152	121	90.8	147
	205	63.4	93	92	154	129	89.2	149
	174	68.2	107	87	122	96	86.5	173
	147	59.2	227	92	104	104	63.5	172
	113	64.7	173	119	79	131	53.2	161
	186	70.4	87	91	142	107	88.0	132
	209	71.3	201	115	182	128	94.7	148
Av.	176	65.6	178	103.6	139.2	118	81.1	160.2
Stand. Dev.	30.22	4.87	17.64	10.15	22.97	12.57	15.52	12.49
				Hay Fever				
	173	68.2	101	112	115	108	92.7	157
	174	73.1	107	87	122	96	86.5	173
	193	75.7	97	103	121	120	89.0	143–
	152	59.6	153	84	158	100	99.5	147
	104	58.7	243	114	139	116	95.7	163
	218	62.6	237	100	93	131	59.8	157
	166	60.8	175	97	152	121	90.8	147
	213	51.8	253	103	173	134	70.2	153
	205	63.4	93	93	154	129	89.2	149
	164	55.6	214	118	137	129	64.2	170
	186	70.4	87	91	142	107	88.0	132
Av.	177	63.6	160	100.2	136.9	117.4	84.8	153.7
Stand. Dev.	30.03	7.20	63.77	10.64	22.28	12.46	12.97	11.22
				Contact Dermatitis				
	197	61.4	186	107	137	115	82.2	142
				Chronic Urticaria				
	190	64.2	137	123	83	142	47.3	139
				Normal				
	149	68.8	167	100	94	123	61.8	143
	178	65.1	176	103	105	125	76.4	154
	127	59.2	137	93	124	133	53.3	178
	157	68.2	164	110	107	124	72.5	158
	168	54.4	114	105	147	119	81.3	156
Av.	156	63.1	151.6	102.2	115.4	124.8	69.1	157.8
Stand. Dev.	17.43	5.97	23.16	5.64	18.49	4.58	9.74	12.21

were combined, evaporated to small bulk (in a stream of CO_2), transferred to a 25 c.c. volumetric flask and made up to volume with petroleum ether. Five cubic centimeter aliquots of this solution were taken for the oxidative determination of the fatty acids and the iodine number determinations.

RESULTS

The results of the analyses are contained in Table I.

(a) No definite differences in the nature of the fatty acids in the three classes of sensitive and in the non-sensitive individuals. Therefore, the earlier finding is confirmed—that there is no essential abnormality in the degree of unsaturation of any of the plasma fatty acids in allergic individuals.

(b) Marked differences in the degree of unsaturation of the fatty acids in the three groups of compounds, the fatty acids being much more unsaturated in the cholesterol esters than in the phospholipids and neutral fat, and somewhat more unsaturated in the phospholipids than in the fat. These results indicate a special function of cholesterol in relation to the metabolism of the unsaturated acids.

REFERENCES

1. Bloor, W. R.: J. Biol. Chem. **82**: 273, 1929.
2. Bloor, W. R.: J. Biol. Chem. **77**: 53, 1928.
3. Yasuda, M.: J. Biol. Chem. **94**: 401, 1931.
4. Smith, R. and Marble, A.: J. Biol. Chem. **117**: 673, 1937.

SERUM CHOLESTEROL IN ALLERGY*

ROBERT CHOBOT, M.D., AND HAROLD D. DUNDY, M.D.
NEW YORK, N. Y.

IN AN endeavor to ascertain the relative merits of the contention that allergy, as manifested by hay fever and asthma, is on an endocrinopathic basis, especially as related to the thyroid, we have done blood studies on a number of children, with particular reference to serum cholesterol. It is a widely accepted belief that serum cholesterol figures bear an inverse relation to thyroid activity, i.e., high cholesterol indicates hypothyroid states—low cholesterol indicates hyperthyroid states.

Barbour[1] has repeatedly claimed excellent results in the treatment of asthmatic children by the feeding of whole thyroid and suprarenal substance. Keen and Teller,[2] on the other hand, found that thyroid therapy had no appreciable effect.

Cameron[3] reports no deviation from the normal in allergic individuals so far as cholesterol is concerned. Moehlig[4] did cholesterol determinations in 27 cases of migraine, with a range from 171 to 300 mg. per 100 c.c., with an average of 225 mg. Fornet, Beno, and Dzsinich[5] found a hypercholesteremia in every attack of asthma and in many, claimed that injections of cholesterol subcutaneously stopped attacks. Molitch and Poliakoff[6] did a series of cholesterol determinations on 505 boys, with special reference to a division into endocrine and nonendocrine groups, and found essentially normal figures, even in the obvious endocrine children. Bullen and Bloor[7] found normal cholesterol figures in a series of 14 cases.

PROCEDURE

Blood was taken from 35 ambulatory allergic children and serum cholesterol (Sackett-Bloor Method),[8] calcium (Clark-Collip Modification of the Kramer and Tisdall Method),[8] and phosphorus (Benedict-Theiss Method)[8] determinations were made.

Similar studies were done on 25 nonallergic children from the wards. Those children of the first group whose cholesterols were over 200 mg. per 100 c.c. were given thyroid extract by mouth, and a careful check was made of their height, weight, pulse rate, and clinical course for six weeks.

In the allergic children, the serum cholesterol determinations ranged from 115 mg. up to 305, mg., with an average for the group of 196 mg. per 100 c.c. There were 23 below 200 mg. and 12 above 200 mg. In 34 calcium determinations, the range was from 9.0 to 11.6 mg., with

*From the Pediatric Asthma Clinic of New York Post-Graduate Medical School and Hospital.

an average of 10.6 mg. In 33 phosphorus determinations, the range was from 3.5 to 10.0 mg., with an average of 5.6 mg. There were 2 below 4.0 mg., 9 between 4.0 and 5.0 mg., and 22 above 5.0 mg.

TABLE I

Calcium, Phosphorus, and Cholesterol Determinations on 35 Allergic Children

RESULTS NO.	NAME	SEX	AGE	CA.	P.	CHOL.	DIAGNOSIS	RESULTS OF THYROID THERAPY
1	A. J.	M	8	11.0*	5.2*	185*	Infectious asthma Eczema	
2	G. G.	F	8	10.8	5.7	230	Eczema	Improved
3	G. S.	M	6	10.1	4.9	210	Asthma—Inhalant B.M.R. -18	No improvement
4	B. W.	M	8	10.3	4.9	240	Infectious asthma	No improvement
5	J. P.	M	7	10.7	6.9	155	Asthma—Pollen and infectious	
6	B. P.	M	12	9.6	6.1	190	Hay fever and asthma	
7	S. R.	F	4	11.1	6.5	170	Asthma—Inhalant	
8	A. D.	F	6	10.8		190	Asthma—Inhalant	No improvement
9	R. J.	M	12	9.8	5.3	115	Hay fever and asthma	
10	A. L.	F	12		5.8	175	Asthma—Infectious	
11	C. D.	F	6	10.8	5.7	170	Asthma	No improvement
12	D. C.	M	12	10.6	5.7	200	Asthma—Inhalant	No change
13	F. G.	M	8	10.8	6.7	165	Asthma	
14	A. P.	M	10	9.6	6.7	165	Infectious asthma	No improvement
15	R. M.	M	5	9.0	6.2	270	Asthma—Inhalant	No improvement
16	A. C.	M	13	10.5	6.6	250	Asthma—Inhalant	Unimproved
17	R. S.	M	6	10.6	6.8	195	Asthma—Inhalant	No change
18	S. R.	M	8	10.6	6.2	170	Asthma	
19	S. B.	M	6	10.7	5.8	150	Eczema and asthma	
20	T. R.	F	10	10.9	4.5	185	Hay fever and asthma	
21	R. L.	M	11	10.7	3.7	150	Asthma—Inhalant	
22	R. S.	M	7	11.2	4.1	195	Asthma	
23	J. F.	M	11	11.0	3.1	150	Hay fever and vasomotor rhinitis	
24	B. C.	F	9	10.3	5.1	180	Asthma—Infectious	
25	M. S.	M	11	11.1	4.0	150	Hay fever	
26	W. S.	M	9	10.5	4.4	210	Asthma—Inhalant and infectious	No improvement
27	J. S.	M	14	10.7	8.9	145	Asthma—Inhalant	
	(Phosphorus duplicated)							
28	J. M.	M	6	10.4	10.0	190	Asthma—Eczema	
	(Phosphorus duplicated)							
29	A. C.	M	13	10.5	4.7	230	Asthma—Hay fever	
30	W. H.	M	9	10.4	4.9	180	Vasomotor rhinitis	
31	R. P.	M	8	11.2	4.5	245	Asthma—Inhalant	Could not tolerate
32	E. D.	M	7	11.0	5.5	305	Asthma—Infectious	Improved
33	M. B.	M	12			230	Nasal mucous membrane suggestive of allergy. No frank clinical picture	
34	R. R.	F	8	10.7		240	Vasomotor rhinitis	
35	F. O.	M	5	11.0	5.1	200	Asthmatic bronchitis	No change

*Values given in milligrams per cent.

In the 25 nonallergic children, the range was from 120 to 200 mg. per 100 c.c. The serum calcium determinations ranged from 9.6 to 11.3 mg.; the phosphorus from 4.4 to 5.2 mg.

Fourteen children were fed thyroid substance with improvement noted in 2 cases, intolerance in 1, and no change in the remaining 11.

DISCUSSION

It has been shown by several observers[9, 10] that blood cholesterol determinations are an unreliable index of thyroid activity, although the general trend of opinion has been to the contrary. We cannot, in this paper, come to any conclusion on this point, except that even when blood cholesterol was elevated, the use of thyroid was of no particular value in the majority of cases.

We cannot explain the high phosphorus figures obtained on other grounds than possibly a low diffusible blood calcium, even though the total serum calcium was normal.

CONCLUSIONS

1. Thyroid therapy in allergic children is of no particular value.
2. Elevation of blood cholesterol is an unreliable guide for the administration of thyroid to allergic children.

REFERENCES

1. Barbour, O.: Arch. Pediat. **53**: 203, 1936.
2. Keen, R. A., and Teller, I.: J. ALLERGY **2**: 488, 1931.
3. Cameron, H. C.: British Medical Association Lecture on Underlying Disturbances of Metabolism of Nervous Child, Brit. M. J. **1**: 185, 1929.
4. Moehlig, R. C.: Endocrinology **15**: 11, 1931.
5. Fornet, B., Beno, P., and Dzsinich, A.: J. A. M. A. **93**: 626, 1929.
6. Molitch, M., and Poliakoff, S.: Arch. Pediat. **53**: 613, 1936.
7. Bullen, S. S., and Bloor, W. R.: J. ALLERGY **8**: 42, 1937.
8. Mattice, M. R.: Chemical Procedures for Clinical Lab., Philadelphia, 1936, Lea & Febiger.
9. Gilligan, D. R., Volk, M. C., Davis, D., and Blumgart, H. L.: Arch. Int. Med. **54**: 746, 1934.
10. McGee, L. C.: Ann. Int. Med. **9**: 728, 1935.

THE SIGNIFICANCE OF DEVELOPMENTAL GROWTH STUDIES IN EVALUATION OF CLINICAL ALLERGY*†

T. WINGATE TODD, CH.B., F.R.C.S., ENG.
CLEVELAND, OHIO

IN HIS address to the British Association last September, Sir Josiah Stamp referred to "the tortuous and baffling art" of transmuting the exact findings of scientists into the wills and lives of unscientific millions and emphasized the need for specialists who treat impact and change as an area of scientific study.[7]

It is because the investigation of allergy whets our appreciation of the significance of constitution that I have found stimulus and encouragement in this particular specialty of medicine. We have, of course, in the past, given far too much attention to the study of disease and far too little to the study of health so that while we recognize stages of illness we are unfamiliar with degrees of health. Yet, we recognize quite clearly that the result of shaking a stick at a dog depends less on that gesture than on the condition of the animal at the moment.[4] What is true of the dog is true of the human being. The impact of a stimulus may be far less significant than the condition of the organism which receives the stimulus. Certainly this is true in allergy. Hence, consideration of the constitution becomes of the greatest importance, and characteristics which never project themselves into a clinical examination may dominate the growth, health, and attitude of the individual. A definition of optimum in either of these aspects of life involves consideration not so much of any so-called norm as of the adjustment of an individual to his environment or the circumstances with which he must cope. Cathcart of Glasgow, writing on the adjustment of mankind to modern industrial conditions, speaks of the advantage possessed by the man of medium size with quick wits and quickly moving muscles in being probably best fitted to cope with the technique of modern industry.[3]

My own observations are limited to the period of childhood and the program of growth and repair so far as it is seen in the first twenty years of life. I think of the adult as revealing in his body and his personality the end-results of that adventure of the early years. So-called individual variation becomes, from this point of view, less the expression of infinite variety than the final result of a trend converging to a common pattern, or in the term of statisticians regression to the mean, modified, perhaps warped and twisted in the course of adventures during the phase of growth and maturation.

*From the Western Reserve University and Associated Foundations.
†Read before the Society for the Study of Asthma and Allied Conditions, New York, N. Y., December 5, 1936.

In the consideration of problems which I wish to emphasize in this communication, it is a question how far we should spread the allergic net and indeed whether we are not actually handicapped by the use of the word "allergy" inasmuch as it has been loosely employed to cover so many aspects of constitutional sensitivity. Alvarez and Hinshaw,[1] in their article on diet last year, point out that there appear many drug-like substances in food which can cause irritation of the bowel or even disturbances at a distance from the abdomen. They also cite fatigue, nervousness, and psychic strain as provocative of sensitivity. It has been our good fortune in Cleveland to watch the stomach and bowel functioning under these complicating influences,[8] and we have drawn up a general statement on the qualifying factors of atmospheric and emotional origin.[9] Queasy stomachs, like stuffy noses, are aggravated on the approach of spring and autumn equinoxes. If, however, we substitute the term sensitivity for allergy we save ourselves the delay of arguments only partially relevant.

Many of the children in the longitudinal study of our Associated Foundations show a very definite progressive pattern in their sensitivity. It is obvious soon after birth as pylorospasm or some feeding difficulty more or less related to specific food, often reaching its height at about nine months of age; progressing to rashes and eczemas of infancy and what is called a "wet" baby; apparently clearing somewhat during the second year but followed at this time by a stuffy nose, mouth habits like thumb-sucking and by adenoid overgrowth, querulousness, and apprehensiveness; succeeded in the third year by seasonal fluctuations in weight, by sudden attacks of gastrointestinal disturbance with high fever, and the beginnings of turbinate congestion, morning sneezing, and nasal discharge. There are considerable nervous tension, restlessness, short attention span, distractibility, and alternations of high spirits with fatigue and overstrain. We have followed these children through preschool and grade school phases and have picked up the record in their older siblings as it continues into and through adolescence. We have followed, step by step, the imprint of this strain of sequence on the bodily growth comparing it with like studies made on children apparently free from such sensitivities.

I can best commence the recital of those physical imprints by comparing the faces, skulls, and throats of two men well advanced in years whose features typify a contrast in lineaments.

FACIAL FEATURES

Cadaver 2881 shows a sensitive, refined, intellectual, and dignified face: cadaver 2497 expresses dullness, insensitivity, gross stupidity. The skull of the first has a narrow high palate, restricted dental arch, and poorly developed facial skeleton; the latter has a broad flat palate, ample dental arch, and well-developed facial skeleton. The nasopharynx

of the first is clear, that of the second is choked by a fleshy adenoid mass. The stupid, dull expression of the second is the adenoid face; the sensitive features and incompletely expanded jaws of the first are the allergic face of which Dr. Duke speaks. These two examples present the end-results of contrasting facial growth patterns as we see them in childhood. Not that the first is uncomplicated by adenoid overgrowth nor that the second invariably presents an adenoid. The adenoid of the first in childhood is an edematous growth which subsides, when curetted, to a formless fragment of tissue. The adenoid of the second is a fleshy mass which lends itself most satisfyingly to exhibition on removal. It is characteristic of the first that adenoid overgrowth will recur after removal, but the fleshy mass of the second does not recur.

Ivor Griffiths has shown that in many cases adenoid overgrowth is associated with sinus disturbance.[5] It is the type of adenoid exemplified by our cadaver 2881 and occurs in children characterized by those sensitivities which I have listed. This type of adenoid recurs after operation and subsides without treatment, fluctuating in size with the condition of nose and sinuses.

That these fluctuations can be shown by roentgenography has been demonstrated by my colleague Dr. Broadbent by a specialized technique in the Bolton Study of the Associated Foundations carried on in our Laboratory of Anatomy.[2] That it is the adenoid which we are observing is easily proved by the roentgenographic appearance of the nasopharynx before and after adenoidectomy.

THE NASOPHARYNX

This brings us to a further consideration of the nasopharynx which can be very clearly studied by roentgenography. On a properly processed x-ray, the lateral wall of the nasopharynx should clearly show Eustachian tube (auditory tube), Eustachian cushion (*torus tubarius*), and fossa of Rosenmüller (lateral recess). These features should be evident not only in adolescence but in childhood and in infancy. If they are obscured one must differentiate between the obscuration due to enlarging adenoid and that resulting from a dense and boggy nasopharyngeal wall.

As the allergic sensitivity clears, the several features of the nasopharynx listed above become visible and thus objective registration can be made of the change in pharyngeal health accompanying subsidence of clinical symptoms.

THE TURBINATES

It will not be necessary to draw attention to the changes in appearance of maxillary sinus with fluctuations in congestion and thickening of mucosa for these appearances are well known. But it is worth while showing the dense outline of congested turbinates on lateral view. Clear

definition of a dense turbinate on a lateral roentgenogram is evidence of an advanced stage of congestion. The anteroposterior roentgenogram shows the intermediate stages. An inferior turbinate which has not undergone chronic congestive disturbance shows quite clearly the whorl of the concha covered on both sides by the sinusoid tissue and mucosa. Thickening of these soft tissues is the first stage in the congestive process. Then comes hypertrophy of the soft tissue, obliteration of the concha, and finally a dense more or less homogeneous mass which narrows or chokes the nasal passage.

The progressive overgrowth of turbinates can have quite a pronounced effect upon the septum and produces sigmoid contour or frank deflection though one would not claim turbinate hypertrophy as the sole cause of septal deviations.

FACIAL GROWTH

Associated with but not necessarily a consequence of this turbinate disturbance is failure of proper facial growth in the nasal area. One should rather ascribe both defects to a common cause for the deficiency in facial growth is already apparent in the first year. Vertical growth of the face and its forward projection are both retarded resulting often in a narrow pinched nose and constriction of upper dental arch so that there is inadequate space for lodgment of the developing and erupting teeth. This results in an orthodontic problem often baffling in its intractability to the current methods of orthodontic treatment.

During the first year, sensitivity is usually most clearly evident in the gastrointestinal tract, and it is to this origin that we should ascribe the beginning of defect in facial growth, a defect which may persist through life and gives the allergic facies, often wrongly characterized as an adenoid countenance.

FLUCTUATIONS IN WEIGHT

During the period when gastrointestinal sensitivity is most pronounced, the weight gain is least. Thus children with a winter allergy put on less weight in winter than in summer, whereas children with a summer allergy put on less weight in summer than in winter. Hence, sensitive children show seasonal fluctuations in weight, producing disturbances of the height-weight ratio.

SCORINGS ON THE BONES

Subclinical disturbances in the gastrointestinal tract are betrayed by a watered silk appearance in the growing ends of the long bones, particularly the lower end of tibia. Such scorings do not necessarily persist, and their number fluctuates with the constitutional disturbance. They are few when the allergy is masked, multiple when it is active.

GROWTH IN STATURE

These scorings can easily be distinguished from the transverse lines or scars produced by definite acute disturbances of health. Growth seems to proceed on the "all-or-nothing" principle and usually, even in the presence of a definite scar, growth is inhibited for a very short time only, perhaps a matter of days. Consequently the scars can be used as an index of the velocity of growth. In nonallergic children during the grade school stage, growth proceeds in limbs and trunk in approximately the proportion of 4 to 3. But in children with a pronounced allergic handicap, the proportion of growth in limbs to that in trunk is 2 to 1 or even greater. If the allergy is very severe, growth in stature is also slowed down, and the child is small in stature as well as light in weight.

THE SUBCUTANEOUS, INTERMUSCULAR AND JOINT TISSUES

Another phase of disturbed metabolism than that shown in anomalies of growth is the character of the subcutaneous tissue. A well-processed roentgenogram shows clear distinction between muscle, subcutaneous tissue, and skin. An allergic child, provided the allergy be active, shows a subcutaneous tissue of uniform density so that the marblings of connective tissue and even the dense trails of superficial veins are lost in the general tissue density which permeates also between the muscles and obscures their outlines. It renders the differentiation between skin and subcutaneous tissue faint or even obliterates it altogether. The weight increase in children with dense subcutaneous tissue is quite fluctuant. It is not a solid stable gain of panniculus. But when the allergy is masked or clears, subcutaneous tissue becomes more translucent. Usually this is accompanied by a failure to gain weight or even by actual weight loss. The child, though failing to put on weight, is actually improved in health because the edematous subcutaneous tissue is exchanged for healthy fat.

The bogginess is seen in joints as well as in subcutaneous and intermuscular tissue. A lateral roentgenogram of the knee lends itself well to observations of this type. The knee joint of a nonallergic child presents a clear triangle between patella, femur, and tibia. But if the subsynovial tissues are edematous, this clear triangle is reduced or obliterated.

MINERALIZATION OF BONE

Another metabolic feature which must be mentioned is the mineralization of bone. We shall not take time to describe fully the characters of cancellous tissue. Suffice it at the moment to point out that the *spongiosa* should show a close texture in which the gothic arch striations described as lines of stress and strain are faintly outlined against a more

or less homogeneous gray background of interstitial substance. In early osteoporosis or demineralization, these striations become more clearly evident owing to the loss of interstitial or labile mineral. Further stages in the process are characterized by open texture, by finer, more spidery striations, or by actual interruption in their continuity. The young child is peculiarly susceptible to demineralization and allergic children of the preschool and grade school ages almost invariably show light mineralization during the active phase of gastrointestinal allergy despite mineral therapeusis.

As the allergy clears, mineralization becomes denser. In pure respiratory allergy one must not expect to find demineralization for this is a deficiency mediated through the gastrointestinal tract.

PSYCHOLOGIC RATINGS

Finally we leave the roentgenogram and note what the psychologic records on these children have to tell us about the personality.

It has often been surmised that allergic children show a relatively high I.Q. This is far from the truth. A child severely handicapped by gastrointestinal sensitivity, especially if that sensitivity is pronounced in early infancy when the brain is growing rapidly and therefore vulnerable, is permanently crippled in his mental capacity. If the handicap is minimal in infancy but increases during the preschool stage, no lasting interference in actual mental capacity is produced. But the mental ability may be clouded. As the allergy clears the mental cloud lifts, and thus the child appears to increase rapidly his I.Q.

PERSONALITY RATINGS

I have already mentioned the nervous tension, the distractibility, the restlessness, and short attention span which characterize the allergic child particularly in the preschool stage. These features together with irritability, whining, and proneness to fatigue are often serious domestic problems, especially when the parents, themselves afflicted with allergy, have none too large a stock of patience or tolerance for the exasperations induced by the conduct of the child. The investigation of this phase of our psychologic problem bids fair to receive a stable experimental foundation in the work of Liddell and others at Cornell University.[6] For the present, these features again must be interpreted as clouds on personality. The parents need not expect always to have a puling child for, as the handicap is overcome, the real personality will emerge and the mutual exasperation disappear.

SUMMARY

Developmental growth studies comprising determinations of physical growth, of tissue texture as revealed by roentgenograms, and of psycho-

logic expansion and personality throw significant light on the evaluation of clinical allergy both in the degree to which the constitution is affected and the progress of the allergic handicap.

REFERENCES

1. Alvarez, W. C., and Hinshaw, H. C.: Foods That Commonly Disagree With People, J. A. M. A. **104:** 2053, 1935.
2. Broadbent, B. H.: A New X-ray Technique and Its Application to Orthodontia, Angle Orthodontist **1:** 45, 1931.
3. Cathcart, E. P., Hughes, D. E. R., and Chambers, J. G.: The Physique of Man in Industry, London, 1935, H. M. Stat. Off., p. 33.
4. Dodge, R.: Anticipatory Reaction, Science **78:** 197, 1933.
5. Griffiths, Ivor: The Lymphatic Drainage of the Nasal Sinuses, Report of the Conservator, Royal College of Surgeons, London, 1936, p. 32.
6. Liddell, H. S.: Nervous Strain in Domesticated Animals and Man, Cornell Veterinarian **26:** 107, 1936.
7. Stamp, J.: The Impact of Science Upon Society, Science **84:** 235, 1936; Manchester Guardian Weekly **35:** 218, 1936.
8. Todd, T. W., and Kuenzel, W.: Studies in the Alimentary Canal of Man; XII. The Stomach's Response to the Menu, Proc. Inter-State Post-Graduate Med. Assembly 350, 1935.
9. Todd, T. W.: Visceral Reactivity, Proc. Assn. for Research in Child Development, Child Development Abstracts, 157, 1936.

THE USE OF STAPHYLOCOCCAL TOXOID IN THE TREATMENT OF 100 CASES OF ACNE VULGARIS*

SOLOMON TANENBAUM, M.D., A. L. JOYNER, M.D., J. A. SPEED, M.D., AND K. M. BREMER
DURHAM, N. C.

ACNE vulgaris is a common disfiguring disease of young adults. Staphylococci usually are present in the lesions either alone or with acne bacilli. Vaccines made from the staphylococci, the acne bacilli, or from a combination of both have not produced uniform improvement.

The introduction of staphylococcal toxoid by Dolman suggested a new method of treatment. Dolman[2] obtained excellent results with the toxoid in 6 cases of acne complicated by furunculosis. Murray[6] reported 3 recoveries, and marked improvement in 21 out of 30 cases. Connor and McKie[1] obtained good results in a small number of cases. In contrast to these favorable reports, Kindel and Costello[4] reported unfavorable results in cases of pustular dermatoses.

During the spring of 1936, 146 otherwise healthy university students with uncomplicated acne vulgaris were treated with staphylococcal toxoid. None of the patients received x-ray or any other type of active treatment. They all ate in the university dining hall the same balanced diet, which was relatively high in carbohydrates. They were all instructed to wash their face and other affected parts three or four times a day, using ivory soap without brush or washcloth, and not to mash or prick the lesions.

The "undiluted" staphylococcal toxoid† used in the experiments described in this paper was made from a toxin containing 1,000 skin-necrotizing units per cubic centimeter (as tested in the skin of the rabbit). The detoxification was accomplished with formalin. Staphylococcal toxoid does not cause any cutaneous reaction in normal animals. We do not believe there is a relationship between the cutaneous reaction produced by toxoid in a person sensitive to it and that caused by toxin in the immune animal or human being. This toxoid resembles other toxoids in that it has a definite affinity for antitoxin and produces a relatively high titer of antitoxin when injected into horses and laboratory animals.

Previous experience in this hospital showed that many patients with staphylococcal infections have severe local and sometimes general reactions to either the undiluted or the 1:10 dilution of toxoid. Each patient was given a preliminary test to determine his sensitivity to the

*From the Department of Bacteriology, the Department of Student Health of Duke University School of Medicine and Duke Hospital, Durham, N. C.

†The staphylococcal toxoid used in the study was very kindly furnished by the Lederle Laboratories, Inc., Pearl River, N. Y.

toxoid: 0.1 c.c. of a 1:100 dilution of the toxoid was injected endermically, and the results were read in twenty-four hours in terms of 1-, 2-, 3-, and 4-plus as in the tuberculin reaction. Treatment was started with the 1:1,000 dilution of the original undiluted toxoid when the reaction was a 2- or 3-plus. Those with a 1-plus and a few giving 2-plus were started with the 1:100 dilution. The initial dose was 0.1 c.c., given subcutaneously in the upper arm. The injections were given twice each week, and the dose increased by 0.2 c.c. each time until the patient was receiving 1.0 c.c. of the undiluted toxoid. No unfavorable reactions were obtained by this method.

This report is based on the results obtained in 100 students whose record seemed complete enough to justify comparison.

TABLE I

RESULTS OF TREATMENT WITH STAPHYLOCOCCAL TOXOID

	GROUP 1 90 TO 100 PER CENT IMPROVEMENT	GROUP 2 OVER 50 PER CENT IMPROVEMENT	GROUP 3 50 PER CENT OR UNDER IMPROVEMENT	GROUP 4 NO IMPROVEMENT
Number	9	49	37	5
Average duration of complaint	3.7 years	3.5 years	4.08 years	4 years
Average age	18.8 years	18.6 years	18.8 years	20.2 years

Table I shows the average age of the patient, the duration of the symptoms, and the results of the treatment. Excellent results were obtained in 9 per cent, good results in 49 per cent, some improvement in 37 per cent, and failure in 5 per cent.

TABLE II

RELATION OF IMPROVEMENT OF SYMPTOMS TO THE SIZE OF THE SKIN REACTION

CUTANEOUS REACTION	GROUP 1 90 TO 100 PER CENT IMPROVEMENT	GROUP 2 OVER 50 PER CENT IMPROVEMENT	GROUP 3 50 PER CENT OR UNDER IMPROVEMENT	GROUP 4 NO IMPROVEMENT
	Per cent	Per cent	Per cent	Per cent
1-plus	0	20.8	32.5	60
2-plus	55	45.8	48.6	40
3-plus	45	33.4	18.9	0
4-plus	0	0	0	0

Table II shows the relationship between the degree of sensitivity and the results of treatment. The best results were obtained in those patients who had a 2- or 3-plus reaction to the original cutaneous test, and the poorest results in those who gave a 1-plus reaction. In general, better results were obtained in students with large pustular lesions than in those with small dry pimples.

Table III gives the duration of the treatment and the final strength of the toxoid used.

Dolman[2] followed the results of treatment in patients with chronic staphylococcal infections by titrating the blood for an increase in

TABLE III

FINAL DILUTION OF TOXOID USED AT COMPLETION OF TREATMENT AND AVERAGE TIME TAKEN FOR COURSE OF TREATMENT

HEIGHT OF DILUTION	GROUP 1 90 TO 100 PER CENT IMPROVEMENT	GROUP 2 OVER 50 PER CENT IMPROVEMENT	GROUP 3 50 PER CENT OR UNDER IMPROVEMENT	GROUP 4 NO IMPROVEMENT
	Per cent	Per cent	Per cent	Per cent
Undiluted	78	84	85	40
1:10	22	14	6	20
1:100		2	6	20
1:1000			3	20

staphylococcal antitoxin. In this study the serum of 77 of the patients was titrated for antitoxic value before treatment. All showed some antihemolytic action. On account of conditions beyond our control, we were unable to titrate all the patients after treatment; consequently we are unable to come to any definite conclusions on this subject.

DISCUSSION

Various types of therapy have been advocated in cases of acne vulgaris. The use of soap and water and the observance of simple hygienic measures may effect some improvement. White[7] discusses the use of lotions and dietary measures, and Fox[3] uses vaccines and roentgen ray therapy. Recently Michael[5] reviewed the literature and attempted to evaluate the various methods of treatment.

The treatment with staphylococcal toxoid was not uniformly successful; considerable improvement was observed in 58 per cent of the cases treated. The best results were obtained in the pustular type of acne and in those patients who were markedly sensitive to the toxoid. Results of antitoxin titrations do not show any conclusive evidence that the degree of improvement is correlated with the increase in antitoxic titer.

Seasonal variations of the disease were not taken into account in the present study as it was begun in early spring and terminated at the end of the school term in June.

Group 4, containing five patients, presents data which should be explained further. Two of the patients dropped treatment because they felt they were not getting any benefit from it. One other of this group continued to complain of soreness following injection of the dose, in spite of only a 2-plus initial cutaneous reaction. This explains the low average duration of treatment and also the low percentage which received undiluted toxoid.

SUMMARY

One hundred university students with acne vulgaris were given preliminary skin test with a 1:100 dilution of staphylococcal toxoid and then treated with various dilutions of this material. Excellent results were obtained in 9 per cent, good results in 49 per cent, some improvement in 37 per cent, and 5 per cent showed no improvement.

REFERENCES

1. Connor, J. I., and McKie, M.: Treatment of Superficial Staphylococcal Infection by Toxoid, Brit. J. Dermat. **46**: 20, 1934.
2. Dolman, C. E.: Treatment of Localized Staphylococcic Infections With Staphylococcus Toxoid, J. A. M. A. **100**: 1007, 1933.
3. Fox, H.: The Roentgen Ray Versus Vaccines in the Treatment of Acne, J. A. M. A. **81**: 1417, 1923.
4. Kindel, D. J., and Costello, M. J.: Staphylococcus Toxoid in the Treatment of Pustular Dermatoses, J. A. M. A. **102**: 1287, 1934.
5. Michael, J. C.: Observations on the Treatment of Acne Vulgaris, J. A. M. A. **105**: 327, 1935.
6. Murray, D. S.: Staphylococcus Toxoid, A Clinical Trial, Lancet **1**: 303, 1935.
7. White, C. J.: The Modern Treatment of Acne Vulgaris, M. Clin. North America **18**: 1465, 1935.

DISCUSSION

DR. MARION B. SULZBERGER, AND DR. G. RUBIN, New York.—At the Skin and Cancer Hospital and in my office, Dr. G. Rubin and I have studied intensively a series of about 50 cases which includes acne vulgaris and certain pyodermas. The following are our conclusions based on over two years' experience with staphylococcus toxoid:

1. Practically all previously untreated individuals react to intracutaneous injections of staphylococcus toxoid with a slight immediate wheal and flare.

2. This wheal and flare reaction is due to substances emanating from the culture medium, and is not due to toxin or other substances derived from the staphylococcus.

3. Practically all untreated individuals react with moderate to strong reactions of papular twenty-four-hour tuberculin type to toxoid injected intracutaneously in doses of 0.02 c.c. of a preparation derived from toxin containing 1,000 D.N.U. per c.c.

4. This reaction is not due to culture medium nor to toxin, but is due to nontoxin substances derived from the staphylococcus. It is, therefore, in all probability based upon an allergic skin sensitivity to products of the staphylococcus. This sensitivity is almost universal among the adults in our material.

5. Almost all untreated individuals react with excessively strong reactions of twenty-four-hour type to toxin injected intracutaneously in doses of 0.05 c.c. of a preparation containing 500 D.N.U. per c.c.

6. In our series repeated injections of toxoid regularly reduced the skin reaction both to toxin and to toxoid. In other words, they regularly increased the resistance of the skin to toxin, and regularly "hyposensitized" the skin to toxoid.

7. Our methods of injection of toxoid did not uniformly increase the antihemolysin titer of the blood serum.

8. The reduction of the toxin skin reaction does not necessarily run absolutely parallel to increase of the antihemolysin titer of the blood serum.

9. The reduction of the toxoid skin reaction does not necessarily run absolutely parallel to increase of blood titer.

10. Intracutaneous injection is not as efficacious as subcutaneous injection in raising the serologic antitoxin titer.

11. In our small series therapeutic results seemed better with subcutaneous than with intracutaneous injections.

Dr. Rubin and I reported on many of these findings with staphylococcus toxoid at the meeting of the Association of American Immunologists last year. (Staphylococcus Toxin and Staphylococcus Toxoid; A Comparison of the Skin Test Reactions and Evidence of Intracutaneous Immunization as Shown by Skin Tests, Marion B. Sulzberger and G. Rubin, Tr. Am. Ass. Immunol., 1936, J. Immunol. **30**: 386, 1936.) We can now add the preliminary report of our therapeutic attempts with staphylococcus toxoid, which may be summarized as follows:

CASES	RESULT
25 cases of acne (both cystic and vulgar, refractory to other treatment; observed for over two years)	6 benefited (all cystic acnes in older women)
3 cases of acne varioliformis (resistant to all other therapy)	3 rapidly and strikingly benefited (2-6 injections)
3 cases of hydroadenitis axillaris (resistant to all other therapy)	3 rapidly and strikingly benefited (3-8 injections)
5 cases of sycosis vulgaris (resistant to all other therapy)	2 complete cures 1 great improvement 1 complete failure 1 (now under treatment) striking improvement after 3 injections

I believe that Dr. Tanenbaum and his collaborators are to be congratulated for calling attention to the use of staphylococcus toxoid in acne vulgaris and especially in their conservative conclusions. It is, of course, obvious that acne vulgaris is not primarily a pyoderma, but is based upon an endocrinologic mechanism. It is, therefore, not to be expected that acne vulgaris will be cured by specific immunologic therapy with staphylococcus products, and this is borne out by our experience. In one series the aberrant types, such as the cystic acne continuing or appearing well beyond the age of puberty or adolescence, were those which responded most favorably to staphylococcus toxoid, while ordinary adolescent acne was in general not benefited by this form of treatment.

As we all know, one must be exceedingly careful in evaluating therapeutic measures in acne vulgaris. This is not only a self-limited disease, usually running a course to permanent cure in a period of two to five years, but is also a disease with an extremely erratic course and with marked seasonal and other remissions. I should estimate that almost half of our cases of acne vulgaris show marked improvement during the summer without any treatment whatsoever. Other cases are benefited by simple regular scrubbing with hot soap and water or by changes in environment or in type of occupation.

The conservatism which Dr. Tanenbaum and his collaborators have displayed is, therefore, most essential in considering the benefits derived in acne vulgaris as possibly due to the staphylococcus toxoid injections. We believe, however, that toxoid injections, while certainly not the answer to the acne vulgaris problem, are surely among the best therapeutic measures in the treatment of recalcitrant cases of cystic acne in older patients.

A CORRELATION OF THE CLINICAL AND PATHOLOGIC FINDINGS IN BRONCHIAL ASTHMA*

E. T. THIEME, M.D., AND J. M. SHELDON, M.D.
ANN ARBOR, MICH.

DEATH from bronchial asthma is of rare occurrence. Macdonald,[1] in 1931, reported eight cases from the University Hospital and accumulated 39 cases from the literature in which autopsies with microscopic examination had been made. Since Macdonald's report, 21 additional cases have been recorded: Waldbott, three;[2, 3] Bubert and Warner, one;[4] Michael and Rowe, two;[5] Hansen, one;[6] Brule, and others, one;[7] Antoniazzi, one;[8] Riopelle, one;[9] Wilmer, and others, one;[10] Colton, and Ziskin, nine;[11] Funk and Higgins, one.[12] Careful analysis[13, 14] of the 68 cases has shown that many were not true asthma. Probably in not more than 43 cases can death be said to have resulted from an asthmatic paroxysm. Additional clinical and pathologic reports of death in *status asthmaticus* would seem justified.

The material for this study was gathered from a series of 2,064 autopsies performed at the University Hospital between July, 1932, and April, 1937, subsequent to the report of Macdonald. Seven cases in which death can be laid to asphyxia, during a paroxysm of bronchial asthma are reported in detail (Group I).

In addition, 10 cases that had the clinical criteria of bronchial asthma but died of other causes, were reviewed as to the existing pathology (Group II). As a control to the above group a series of 11 cases showing pathologic changes suggestive of bronchial asthma, but in which death was due to other causes, were studied in regard to their clinical history (Group III).

GROUP I

CASE 1.—R. B., white male, aged eighteen months, was first seen at the University Hospital on August 27, 1933, because of an eczematoid eruption which had been present for three months. Upon changing the formula and treating the lesions locally there was prompt relief of the symptoms. His second admission was on September 23, 1934, because of "asthma and eczema." The asthma dated to October, 1933, when wheezing dyspnea was noticed. Since the onset the attacks had been constantly present.

Physical Examination.—Physical examination revealed a white male of eighteen months in acute respiratory distress. The stature was average and the state of nutrition was good. There was an eczematoid eruption over the head, face, and extremities. The chest was held in the position of inspiration. Typical asthmatic

*From the Department of Pathology and the Department of Internal Medicine, University of Michigan.

Read before the Fifteenth Annual Meeting of the Association for the Study of Allergy, Atlantic City, N. J., June 8, 1937.

râles and rhonchi were heard throughout the lung fields. The heart was overactive, but otherwise was normal. The liver could be felt two fingers breadth below the right costal margin.

Clinical Course.—On admission supportive measures failed to relieve adequately the asthmatic paroxysm. Five hours later while still in an asthmatic attack vomitus was aspirated and the respirations ceased. The heart continued to contract for twelve minutes.

Autopsy.—The body was that of a male infant showing good nutrition. The lungs were markedly emphysematous and many of the bronchi were filled with mucinous plugs. There was moderate edema but no consolidation or purulent exudate was present. The heart weighed 100 gm. The left ventricle averaged 10 mm. in thickness, the right 6 mm. The thymus filled the anterior mediastinum but no compression of the trachea could be demonstrated.

Microscopic Examination.—The myocardium showed moderate hypoplasia. The lungs showed marked emphysema. There was moderate edema, and food particles were seen in the alveoli at both bases. The medium-sized bronchi showed a moderate but very definite hypertrophy of their musculature. The basement membrane was definitely thickened and in areas there was evidence of sacculation. Eosinophilic infiltration was marked in the subepithelial tissue, extending around glands and into the peribronchial tissue. Eosinophiles were also present in mucinous plugs found in the majority of the bronchi. The bronchial glands showed only early changes. There was no evidence of pneumonia. The aorta and adrenal cortex showed slight evidence of hypoplasia. There was a generalized lymphoid hyperplasia most marked in the persistent thymus.

CASE 2.—E. D., female, aged fourteen years, schoolgirl, entered the University Hospital July 10, 1933, complaining of asthma. The patient had been in good health until the onset of a "cold" in 1930. Following the cold there persisted a dry hacking cough particularly noticeable in the early morning. In November, 1931, she had her first attack of tightness in the chest, wheezing, and shortness of breath. These attacks occurred once or twice weekly with occasional attacks lasting continuously for four to five days. It was known that asthmatic attacks were precipitated by one type of tooth paste and by acute upper respiratory infections. The father had had hay fever and asthma, and two older sisters had had hay fever.

Physical Examination.—Physical examination on the last admission, revealed a white female of fourteen years, in a mild asthmatic attack. The pulse rate was 112 per minute, the respiratory rate 28 per minute, and the blood pressure was 120/72 mm. Her stature was average. The state of nutrition was good. The skin was warm and moist. The nasal mucous membrane was hyperemic with a slight seropurulent discharge in both nasal orifices. The chest was slightly emphysematous, characteristic asthmatic râles and rhonchi were heard throughout the lung fields. Expiration was prolonged and was accompanied by wheezing.

Laboratory Examination.—Kahn test, urinalysis, and repeated postanterior stereoscopic roentgenograms of the chest, and x-ray films of the nasal accessory sinuses were negative. Differential blood smears repeatedly showed an eosinophilia of 3 per cent to 8 per cent. Cutaneous skin tests to common allergens were positive for dust, milk, feathers, black pepper, and cucumber. Scratch tests to the tooth paste that had caused asthmatic attacks were weakly positive.

Clinical Course.—On the evening of July 11, 1933, she suddenly developed a severe asthmatic attack. She became nauseated and vomited. Subcutaneous epinephrine in repeated doses gave little relief. She soon lapsed into a coma, the respiratory rate dropped to five to six per minute, the pulse rate increased to 160 per minute, cyanosis then developed in spite of the use of oxygen and she expired

fifteen hours after the onset of the attack. The clinical record revealed that she received morphine sulfate 80 mg., atropine sulfate 2.1 mg., epinephrine hydrochloride 9 c.c., and caffeine sodium benzoate 2.4 gm. over the fifteen hour terminal period.

Autopsy.—The body was that of a well-nourished, adolescent, white female. The lungs were markedly emphysematous and there were many mucinous plugs in the bronchi; very slight evidence of a purulent exudate could be found at both bases. There were no pleural adhesions. The heart weighed 195 gm., the left ventricular thickness averaging 15 mm., the right 7 mm. There was no gross evidence of hypertrophy. The thymic remains were grossly increased.

Microscopic Examination.—There was marked emphysema and evidence of a very early bronchopneumonia. The thickening of the basement membrane and the hypertrophy of the bronchial musculature were marked. The bronchi showed moderate sacculation. The eosinophilic infiltration was definite but patchy throughout the upper and lower lung fields. A large majority of the medium and a few of the larger bronchi showed large plugs of mucinous exudate. The changes in the bronchial mucous glands were moderate. The heart showed only a moderate hyperplasia of an intrinsicly hypoplastic myocardium. The aorta and adrenals were moderately hypoplastic. The thymus were hyperplastic with early fatty atrophy. There were no other pertinent findings.

CASE 3.—S. C., white female, aged twenty-one years, waitress, was first admitted to the University Hospital August 5, 1936, because of severe dyspnea. At the age of seven, she had had her first asthmatic attack, consisting of shortness of breath, wheezing, and cough. The paroxysms occurred at irregular intervals until June, 1936, when they became more frequent and more severe. On November 8, 1936, she developed a persistent asthmatic attack unrelieved by subcutaneous epinephrine and morphine sulfate and so was admitted to the hospital on November 10, 1936. There was no family history of allergic disturbance.

Physical Examination.—Physical examination on the final admission revealed a young, undernourished female, in marked respiratory distress. The oral temperature was 99.0°, the pulse rate 110 per minute, blood pressure 130/80 mm. and the respiratory rate was 40 per minute. There was an audible respiratory wheeze. The skin felt cold and moist and appeared pale. The lips and nail beds were cyanotic. The pupils were small but reacted to light and in accommodation. The chest was markedly emphysematous. Expiration was markedly prolonged. Sibilant and sonorous râles and rhonchi were heard throughout the lung fields. The heart was overactive but otherwise it was normal.

Laboratory Examinations.—Kahn test and urinalysis were negative. Stereoscopic x-ray study of the chest (August 7, 1936) showed bilateral cervical ribs and pulmonary emphysema. The blood examination (August 10, 1936) showed 90 per cent hemoglobin (Sahli), 10,300 W.B.C.; 14 per cent eosinophiles. Scratch tests with whole protein allergens were weakly positive to June grass, timothy grass, and house dust.

Clinical Course.—The patient on admission was in extreme respiratory distress. The course was rapidly terminal, the pulse rate increasing and the respiratory rate decreasing until death occurred ten hours after admission. The heart continued to contract after the respirations ceased. The clinical chart reveals that 6 c.c. of subcutaneous epinephrine, 1:1,000, subcutaneous morphine sulfate 65 mg., and atropine sulfate 2.6 mg. were given over the ten-hour period.

Autopsy.—The body was that of an adult white female in good nutrition. The lungs filled the thoracic cavity overlapping in the anterior mediastinum. The bronchi stood out plainly, many being plugged with mucus. There were no areas of con-

solidation and no exudate. The heart weighed 200 gm., the left ventricular thickness averaged 18 mm., the right 6 mm. The thymic gland filled the anterior mediastinum but had not compressed the trachea. There were no other pertinent findings.

Microscopic Examination.—In the respiratory tract the basement membranes were markedly thickened and hyalinized, not only in the medium-sized bronchi but also in the large bronchi and trachea. The sacculation of the bronchi was marked. Eosinophilic infiltration occurred about all the medium-sized bronchi and the majority of the larger bronchi. However, no infiltration of the cartilage plates was seen. The mucinous exudate that filled most of the bronchi contained many eosinophiles. Many of the bronchial glands showed hypertrophy, widening of their mouths, and increased mucin formation. No evidence of pneumonia could be found. The heart showed some subepicardial fatty infiltration and slight generalized hypoplasia, with, however, small areas of hyperplasia in the left ventricle. The aorta and adrenals were slightly hypoplastic. There was generalized lymphoid hyperplasia, and the thymic remains were very abundant. No other pertinent pathology was found.

CASE 4.—A. J., white male, aged thirty-seven years, farmer, was admitted to the University Hospital on June 19, 1932, because of an infected compound fracture of the left tibia and fibula. The injury had occurred two months previously and no attempt to reduce the fracture had been made. Since infancy he had suffered from attacks of dyspnea, cough, and wheezing, occurring regularly after contact with horses. Asthma had occurred each fall for the past three years.

Physical Examination.—Physical examination revealed a pale, undernourished, adult, white male mentally confused. The chest was emphysematous. Characteristic asthmatic râles and an expiratory wheeze could be heard throughout the lung fields. There was a hand-sized ulcerated area with a purulent discharge situated over the anterior surface of the left leg between the middle and lower thirds. The distal portion of the tibia protruded through the middle of the ulcerated area. Considerable edema of the entire left leg was present.

Laboratory Examination.—Blood Kahn test, urinalysis, and stereoscopic x-ray films of the chest were negative.

Clinical Course.—During the patient's stay in the hospital, three to four typical asthmatic paroxysms occurred daily. These were promptly relieved by subcutaneous epinephrine. However, on July 10, 1936, he developed an asthmatic attack which was unrelieved by subcutaneous epinephrine or oxygen, and death occurred twenty-six hours later in *status asthmaticus.*

Autopsy.—The body was that of an adult white male showing evidence of weight loss. The left leg had been amputated 11 cm. below the knee. The bones presented in the wound, which, however, was clean. The heart weighed 350 gm. The left ventricular thickness averaged 20 mm. and the right 7 mm. There was moderate atherosclerosis of a hypoplastic aorta. The lungs were very emphysematous but contained none of the usual mucinous plugs. The bronchi showed a purulent bronchitis with very early bronchopneumonia but no areas of consolidation. The thymus was fairly large and contained much lymphoid tissue.

Microscopic Examination.—The heart showed no significant changes, the myocardium showing hypoplasia of the muscle fibers. The coronaries were moderately atherosclerotic. The lungs were emphysematous with an early bronchitis and bronchopneumonia. There were no mucinous plugs, the alveoli and bronchi having a purulent exudate only. There was, however, definite hypertrophy of the bronchial musculature, and a thickening of the basement membrane and sacculation of the bronchi. The eosinophilia was definite throughout the lungs. Although of

moderate degree, changes in the bronchial glands were unquestionable. The aorta with moderate atherosclerosis was slightly hypoplastic. The adrenals were markedly hypoplastic. There was a generalized lymphoid hyperplasia. There was a chronic osteomyelitis of the left tibia and fibula.

CASE 5.—A. G. H., a white male, aged forty-one years, carpenter, was admitted to the University Hospital on November 21, 1931, complaining of "asthma." His first attack was at the age of seventeen years, and was precipitated by inhalation of wheat dust. For the following twelve years occasional attacks occurred, usually brought on by inhalation of various dusts, although two severe attacks were initiated by upper respiratory infections. From 1925 to 1930, while living in California, he was entirely free of respiratory symptoms. In 1930, he moved to Michigan and his paroxysms of dyspnea returned. It was thought that sweet potatoes, pork, milk, fish, and eggs would precipitate attacks. The paternal grandmother had had asthma and hay fever, and the maternal grandfather had had asthma.

Physical Examination.—Revealed an undernourished, adult, white male in a moderately severe asthmatic attack. Slight cyanosis of lips and nail beds was present. The chest was emphysematous. Characteristic asthmatic râles were heard throughout the lung fields. The remainder of the examination was essentially negative.

Laboratory Examinations.—Kahn test and urinalysis were negative. The sputum showed numerous organisms and many eosinophiles on direct (Wright) stained smear. Sputum culture showed Streptococcus hemolyticus and Streptococcus viridans. Roentgenograms of the nasal accessory sinuses were interpreted as showing a paranasal sinusitis. Stereoscopic x-ray films of the chest showed emphysema and evidence of chronic recurrent respiratory infections.

Clinical Course.—The usual supportive measures over a thirty-five-day period failed to give adequate relief. It was, therefore, decided to do a bilateral transpleural pulmonary neurectomy. This was done uneventfully in two operations with some temporary improvement. Two days after the second operation, while in an asthmatic seizure he suddenly developed air hunger, became markedly cyanotic and died in a very short time.

Autopsy.—The body was that of an adult white male in poor nutrition. There was a fresh surgical wound along the posterior border of the left scapula. From this incision, subcutaneous emphysema spread anteriorly through the axilla and over the left portion of the head and neck. A left pneumothorax was present. The lungs were emphysematous but showed only a slight amount of mucinous exudate. The heart weighed 370 gm. The left ventricular thickness averaged 25 mm., the right 9 mm. The thymus was identified grossly. Agenesia of the right kidney was noted.

Microscopic Examination.—The myocardium showed a hypoplasia of muscle fibers occasionally a brown atrophy. The lungs had evidence of an early bronchopneumonia and a moderate emphysema. The basement membrane was thickened both in the bronchi and trachea. The muscle hypertrophy and bronchial sacculation were marked. Eosinophilia while marked in some areas was notably absent in others. Many of the medium bronchi contained mucinous plugs with eosinophiles. In some areas there was marked increased mucin formation in the bronchial glands. The aorta was normal in size and there was slight atherosclerosis. The thyroid showed a Graves' constitution adenomatous goiter. There was a generalized lymphoid hyperplasia, particularly marked in the abundant thymic remains. No other significant pathology was found.

CASE 6.—H. E. R., a male, aged fifty-one years, was first seen in the University Hospital May 21, 1935, and subsequently returned for further treatment in November, 1935. Since the age of thirteen years he had suffered from attacks of

paroxysmal dyspnea accompanied by a wheezing cough productive of thick whitish or yellowish sputum. During the last year the attacks were of increasing frequency and severity and had been almost continuous for the past month. There was no family history of allergic disturbances.

Physical Examination.—Physical examination on the last admission revealed a stuporous white male in severe respiratory distress. The skin appeared ashen and was cold and moist. Marked cyanosis was present. There was movement of the alae nasi with each respiratory attempt. The pupils were pin point. The pulse rate was 120 per minute; the respiratory rate 70 per minute, and the temperature was 102.4° (rectal). The chest was barrel-shaped with marked limitation of respiratory excursion. The upper anterior chest was hyperresonant, dulness was present in the right lower lung field and the right axilla. Moist râles could be heard at the left base and at the apex of the left axilla. The breath sounds were bronchial in type. All normal reflexes were absent or greatly reduced.

Laboratory Examinations.—Kahn test and urinalysis were negative. The white blood cell count was 17,750 with 85 per cent polymorphonuclear leucocytes. Cutaneous and intracutaneous skin tests to common antigens in June, 1935, were positive to clam, crab, lobster, oyster, lactalbumin (bovine), barley, tobacco, flaxseed, cow dander, and feathers.

Clinical Course.—The patient was stuporous when first seen. He gradually went into a deep coma, the respirations became slower and more shallow. A respiratory death occurred four hours after admission. It is important to note that morphine sulfate, 32 mg., was given forty-five minutes previous to his admission to the hospital because of the severe *status asthmaticus.*

Autopsy.—The body was that of an adult white male in good nutrition. The thorax was in the inspiratory phase. The lungs were emphysematous, many of the bronchi were dilated with mucoid and purulent fluid. There was evidence of early bronchopneumonia. There were no areas of frank consolidation. The heart weighed 290 gm., the left ventricular thickness measured 18 mm., the right 10 mm. Grossly, the right ventricle was considered hypertrophied.

Microscopic Examination.—The right ventricle showed moderate hyperplasia, and the coronaries had the changes of early atherosclerosis. The lungs demonstrated all the expected changes of bronchial asthma combined in many areas with the bronchopneumonia. Although the hyaline thickening of the basement membrane and the eosinophilia were often not prominent, the hypertrophy of the bronchial muscle was marked throughout. Sacculation and changes in the mucous glands were hard to demonstrate. However, even in the purulent exudate of the bronchopneumonia, mucinous plugs of the type of Curschmann's spirals could be seen. The atherosclerosis of the aorta was slight. There was no generalized lymphoid hyperplasia, and the thymus showed advance fatty atrophy. The adrenals were hypoplastic.

CASE 7.—J. H. male, aged fifty-nine years, railroad shopman, entered the University Hospital June 1, 1931, complaining of attacks of shortness of breath and coughing. The past history was negative except for attacks of rheumatic fever at ages thirteen and twenty years. The family history was negative for allergic diseases. The patient had enjoyed good health until July, 1930. At this time he developed a "cold," which was soon followed by attacks of coughing, wheezing, and shortness of breath that persisted until the time of admission. The attacks were chiefly nocturnal lasting one to two hours but could be relieved in five to ten minutes by subcutaneous epinephrine.

Physical Examination.—Physical examination on admission revealed an elderly white male in respiratory distress. Nutrition was good. The lips and nail beds were slightly cyanotic. The left naris was partly obstructed, and a slight amount

of mucopurulent exudate was present in both nares. The teeth showed poor hygiene, but no purulent foci were found in the mouth. The chest was markedly emphysematous. Characteristic asthmatic râles and rhonchi were heard throughout both lung fields. The heart appeared slightly enlarged to the left but otherwise it was normal.

Laboratory Examination.—The Kahn test was negative. Concentrated sputum was negative for acid fast bacilli. The urine showed a trace of of albumin. Eosinophiles were present in the blood to the extent of 11 per cent. Roentgenologic study of the nasal accessory sinuses was negative. Stereoscopic roentgenograms of the chest showed healed bilateral upper lobe tuberculosis. Cutaneous and intracutaneous tests to 150 common allergens were negative.

Clinical Course.—Symptomatic treatment, consisting of subcutaneous epinephrine and foreign protein shock, afforded relief for periods of three to eleven days. However, each recurrent attack was more severe and more prolonged until on August 15, 1931, the paroxysms became continuous. Death occurred eighteen hours later in *status asthmaticus.*

Autopsy.—The body was that of an adult male in good nutrition. Slight clubbing of the fingers was noted. The heart was grossly enlarged and weighed 420 gm., the left ventricle averaged 20 mm., the right 10 mm. Both were considered hypertrophied. The lung borders overlapped in the anterior mediastinum. The lungs were emphysematous and thick tenacious mucus could be expressed from the bronchi. There was a large calcified tubercle in the right apex. A colloid goiter and a cystic glandular hyperplasia of the prostate were also described.

Microscopic Examination.—The myocardium showed hypoplastic muscle fibers, with further brown atrophy. There was a very early bronchopneumonia in addition to the complete picture of bronchial asthma. Everywhere there were marked thickening of the basement membrane, hypertrophy of muscle, sacculation of bronchi, eosinophilic infiltrations, typical abundant mucus and exudate, and dilation of the bronchial glands. This was the only case in which the sections demonstrated eosinophilic infiltrations of the bronchial cartilages. The aorta and adrenal medulla were moderately hypoplastic. There was a generalized lymphoid hyperplasia but very little thymic tissue was present. The arteries showed a generalized arteriosclerosis and the prostate a cystic glandular hyperplasia.

DISCUSSION

From the clinical standpoint each of these seven cases has fulfilled the diagnostic criteria of bronchial asthma. They all died from immediate results of an asthmatic paroxysm. The age of this group varied from eighteen months to fifty-nine years. The duration of asthma varied from thirteen months to thirty-eight years. Five of the seven cases were known to be sensitive to extrinsic proteins, and asthmatic attacks in five of the cases were initiated by respiratory tract infections. In six of the seven cases adequate trial of the usually accepted supportive measures failed to give symptomatic relief. One case (6) entered the hospital in a moribund state from which the usual supportive measures would not revive him. Undoubtedly the use of an excessive dose of morphine sulfate immediately prior to his hospital entry was contributory to his terminal asphyxia. In cases 2 and 3 morphine and atropine may also be considered contributory factors in the cause of death. Morphine depresses the respiratory center and the cough reflex, thus

permitting the accumulation of bronchial secretions. Atropine, tending to thicken the bronchial secretions, increases the difficulty in raising the mucous plugs. These combined actions of the two drugs decrease the respiratory efficiency and contribute toward the terminal asphyxia. It is our opinion that atropine and morphine should never be used in status asthmaticus. If these drugs are used in the management of milder asthmatic paroxysms, they should be given with extreme care and then only in small doses.

Pathology.—Complete autopsies were performed in four instances and complete autopsies with the exception of the brain were done in the other three. The pulmonary findings in our group were in entire agree-

Fig. 1.—(Case 3), Section of medium-sized bronchus ×90. Note marked hyaline thickening of the basement membrane, hypertrophy of the bronchial musculature, sacculation of the bronchus, and moderate eosinophilic infiltrations. The mucinous plug partially filling the bronchus contains many eosinophiles.

ment with the reports of Macdonald,[1] Huber and Koessler,[15] Kountz and Alexander,[16] Rackemann,[13] and others. Microscopically the findings consisted of hyaline thickening of the basement membrane, hypertrophy of the musculature of the medium bronchi, sacculation of the bronchi, eosinophilia of the submucosa and peribronchial tissue, mucinous exudate (often twisted into Curschmann's spirals) completely plugging many of the bronchi, widening of the mouths of the mucous glands with excessive mucin production. The photomicrograph (Fig. 1) taken from Case 3 illustrates most of these findings.

All seven of our cases uniformly showed these findings. We have not attempted accurate measurement of bronchial wall thickness as done by

Huber and Koessler, Kountz and Alexander, and others[4] because of technical difficulties and the uncertainty of their values. In addition we do not wish to emphasize any one finding but rather the entire pathologic picture.

Associated Pathology.—There has been disagreement as to the presence or absence of right ventricular hypertrophy in long-standing bronchial asthma. Alexander and others,[17] Paul,[18] and Hansen and Colton

TABLE I

CARDIAC STATUS

CASE NUMBER	AGE	DURATION OF DISEASE	TERMINAL CONDITION	LEFT VENTRICULAR WALL	RIGHT VENTRICULAR WALL	HEART WEIGHT	OTHER CARDIAC CHANGES
	yrs.	yrs.		MM.	mm.	gm.	
1	1½	1	Asthmatic paroxysms. Aspiration of emesis	10	6	100	Moderate hypoplasia of myocardium
2	14	2	*Status asthmaticus*	15	7	195	Moderate hyperplasia of an intrinsicly hypoplastic myocardium
3	21	14	*Status asthmaticus*	18	6	200	Hypoplasia but small areas of left ventricle hyperplasia
4	37	37	Death in an asthmatic attack	20	7	350	Hypoplasia of muscle fibers
5	41	23	*Status asthmaticus*	25	9	370	Hypoplasia of muscle fibers. Brown atrophy showing a previous hypertrophy which is still present in many sections
6	51	38	Bronchopneumonia and asthmatic paroxysms	18	10	290	Hypertrophy of right ventricle. Slight coronary sclerosis. Slight myocardial fibrosis
7	59	1½	Asthmatic paroxysms. Terminal cardiac failure	20	10	420	Coronary sclerosis. Brown atrophy and hypertrophy both left and right ventricles

found the heart remarkably free from abnormal changes in uncomplicated asthma. Macdonald found both left and right ventricular hypertrophy in the majority of his eight cases. In our group all of the cases were surprisingly free from cardiac abnormalities.

Quantitative evaluation of the myocardium may be difficult in view of the hypoplasia expected with the thymicolymphatic constitution. This latter syndrome was a uniform finding in the patients described from this hospital by Macdonald, but has not often been considered by other writers. The abundant thymic remains, hypoplasia of aorta, adrenals and myocardium, and the generalized lymphoid hyperplasia

TABLE II

EVIDENCE OF THYMICO-LYMPHATIC CONSTITUTION

CASE NUMBER	THYMUS	LYMPHOID TISSUE	ADRENALS	AORTA
1	Lymphoid hyperplasia of a persistent thymus	Generalized hyperplasia	Hypoplasia of cortex	Slight hypoplasia
2	Hyperplastic thymus with early fatty atrophy	Generalized hyperplasia	Hypoplasia most marked in medulla	Hypoplastic
3	Abundant remains grossly	Generalized	Slight hypoplasia	Slight hypoplasia
4	Fairly large remains, abundant lymphoid tissue	Generalized increase	Marked hypoplasia of medulla	Hypoplastic
5	Abundant remains. Little atrophy	Hyperplastic throughout	Hypoplasia of medulla	Essentially normal
6	Advanced fatty atrophy	No increase	Hypoplasia	Atherosclerosis
7	Slight remains	Generalized hyperplasia	Hypoplasia of medulla	Moderate hypoplasia

have been the rule in our cases. Table II is a summary of the evidence of thymicolymphatic constitution. It will be seen that the cases are fairly uniform with one exception (6) which is lacking in these evidences.

These cases are remarkable in that there was no complicating pathology of importance other than the one case (4), which had chronic osteomyelitis of the leg.

Waldbott[2] in a study of deaths in infantile asthmatics found as outstanding features hemorrhagic exudate, capillary congestion, degeneration of alveolar cells, and traumatic emphysema alternating with atelectasis. In an infant, aged eighteen months, Case 1 in our series, none of these features were paramount. In our case the gross and microscopic findings were similar to those of the adults. We are unable to explain these divergent findings unless by differences in the duration and severity of the disease.

GROUP II

The following ten reports are from cases in which there was good clinical evidence of bronchial asthma but death resulted from other causes. Brief summaries of the protocols of the complete autopsies are given.

CASE 1.—H. F. a white male, aged seventy-nine years, was admitted to the medical service of the University Hospital because of dyspnea, palpitation, and precordial pain on exertion. For forty years he had had attacks of wheezing and dyspnea ending in the production of thick yellow sputum. Since April, 1934, the attacks had been more severe and more frequent, occurring three to four times a week. There was no known allergic manifestation in the family. Examinations revealed arteriosclerotic heart disease, auricular fibrillation, and cardiac failure. The chest showed musical râles and expiratory wheezes typical of bronchial asthma. The differential blood smear showed a 9 per cent eosinophilia. Eleven days after admission a cardiac death occurred.

Autopsy.—The essential findings at autopsy were generalized arteriosclerosis, and arteriosclerotic heart disease with many anemic infarcts of the left ventricle. The lungs were emphysematous without evidence of mucinous plugs. There was moderate thickening of the basement membrane in the larger bronchi only, and slight peribronchial eosinophilia. No other pulmonary changes were present except purulent bronchopneumonia.

CASE 2.—H. C. C., a white male, aged sixty-two years, was admitted to the surgical service of the University Hospital on April 22, 1935, because of a fractured left hip. For fifteen or twenty years he had had paroxysmal attacks of shortness of breath, wheezing, and cough, productive of a foamy sputum. The physical examination in addition to the fracture of the left hip revealed an emphysematous chest and characteristic asthmatic râles and rhonchi. During his stay in the hospital there occurred daily attacks of wheezing respiration that were promptly relieved by epinephrine. On April 29, pneumonia developed from which he succumbed on May 5, 1935. Blood eosinophilia was not present. None of his family was known to have had allergic disease.

Autopsy.—Grossly there was a fracture of the left femur. Microscopically there was generalized arteriosclerosis and lobar pneumonia with chronic tracheobronchitis. Also a pulmonary embolism had occurred. The lungs showed marked hyaline thickening of the basement membrane in the large bronchi and trachea. Many of the bronchi contained pus but a few also showed increased mucin.

CASE 3.—G. K., a white female of fifty years, entered the University Hospital on June 15, 1935, because of epigastric pain, nausea, and vomiting. Since the age of three years, each spring and each fall, she had had paroxysmal attacks of wheezing respiration and cough that were promptly relieved by epinephrine.

Physical Examination.—Physical examination revealed an emphysematous chest. Coarse and fine râles and an expiratory wheeze were heard throughout the lung fields. On palpation, tenderness was elicited in the epigastrium. On August 13, 1935, a left-sided hemiplegia developed. Death occurred six days later.

Autopsy.—Microscopically, the generalized arteriosclerosis was marked with evidence of many old and fresh cerebral hemorrhages. The heart was enlarged and there were many myocardial infarcts. The lungs also showed infarcts, bronchopneumonia, and embolism. There was moderate thickening of the basement membrane of the medium-sized bronchi only.

CASE 4.—A. H. G., a white male, of eighteen years, was admitted to the medical service of the University Hospital on November 5, 1935, because of chest pain, cough, and fever of some two weeks' duration. Since an infant he had had attacks of dyspnea, wheezing, and coughing, which occurred without seasonal incidence every four or five months. He was known to be sensitized to corn, wheat, and beets. The examinations showed an unresolved pneumonia, bronchiectasis, and empyema from which exitus occurred on November 9, 1935.

Autopsy.—The pulmonary findings were the most important, the lungs showing unresolved pneumonia, bronchitis, bronchiectasis, and hyaline thickening of the basement membrane of the large and small bronchi, also sacculation of the bronchi and trachea. The heart showed moderate left ventricular hypertrophy.

CASE 5.—R. E. F., white male, aged fifty-five years, was admitted to the University Hospital on April 28, 1936, complaining of weakness, abdominal distension, and abdominal pain. He had also had paroxysmal attacks of shortness of breath with wheezing and cough productive of white frothy sputum. The dyspneic attacks had been present for two years. They were chiefly nocturnal but on occasion they occurred during the day. The attacks would last three to four hours but could be

relieved promptly with adrenalin. The examination revealed a secondary anemia, cirrhosis of the liver, and an intrinsic asthmatic bronchitis. Bronchopneumonia developed from which death occurred on June 6, 1936.

Autopsy.—The liver showed an atrophic cirrhosis with an active chronic purulent cholecystitis and ascending purulent cholangitis. Also there was a generalized peritonitis. The lungs showed moderate bronchiectasis, aspiration pneumonia, and occasional slight hyaline thickening of the basement membrane of the large bronchi.

CASE 6.—A. A. H., a white male, aged fifty-one years, was admitted to the University Hospital on May 19, 1936, complaining of weakness, swelling of the ankles, pallor, and asthma. Since the age of sixteen years he had had repeated attacks of wheezing and dyspnea accompanied by a cough which was productive of white frothy sputum. His last attack occurred on May 18, 1936. The examinations revealed an advanced glomerular-tubular nephritis, uremia, and bronchial asthma. Death occurred as a result of renal insufficiency on June 2, 1936.

Cutaneous skin tests were positive to feathers, house dust, and animal danders. The differential blood smear showed a 4 per cent eosinophilia at the time of admission.

Autopsy.—At autopsy chronic glomerular-tubular nephritis was found. In addition there was a chronic fibroid pneumonia and early terminal purulent bronchitis. The basement membranes of medium-sized bronchi showed occasional thickenings.

CASE 7.—V. A., a white female of thirty-eight years, was admitted to the gynecological service of the University Hospital on June 24, 1934, because of vaginal bleeding, loss of weight, pallor, and weakness. For the past eight years she had repeated attacks of wheezing and dyspnea occurring with variable frequency and variable severity. The attacks were always relieved promptly by subcutaneous epinephrine.

The examination showed a carcinoma of the cervix, secondary anemia, emaciation, and pulmonary emphysema. Death occurred on November 28, 1934.

Autopsy.—The autopsy confirmed the far advanced carcinoma of the cervix with multiple metastases, not, however, to the lungs, which showed only slight thickening of the basement membrane of the large bronchi.

CASE 8.—J. E., a white male, aged forty-seven years, was admitted to the University Hospital on August 26, 1935, because of chest pain, weakness, cough and asthma. For the past twenty-five years he had suffered from paroxysmal attacks of shortness of breath with wheezing. The attacks occurred from late August to frost, each year, and were accompanied by characteristic hay fever. His asthma was relieved when he stayed in northern Michigan during the summers of 1929 and 1930.

The examinations revealed a bronchogenic neoplasm, left bronchopleural fistulae, emaciation, and a thrombosis of the left internal jugular vein. A right hemiplegia developed and death occurred on November 23, 1935.

Cutaneous skin tests to 150 common allergens were strongly positive to short and long ragweed pollen, horse dander, and hog dander.

Autopsy.—The autopsy showed a primary bronchogenic carcinoma with multiple metastases, bronchitis, and bronchopneumonia. No changes usually associated with asthma were present, and no cardiac hypertrophy was noted.

CASE 9.—E. P., a white female, aged thirty-five years, was admitted to the University Hospital in January, 1936, because of abdominal pain and jaundice. For a number of years she had had attacks of wheezing and dyspnea, occurring only during the summer months. The attacks were relieved by subcutaneous epinephrine or by residing in northern Michigan.

The examinations revealed the signs and symptoms of a common duct stone, jaundice, and an emphysematous chest. Following an abdominal laparotomy a bronchopneumonia developed from which death occurred on March 8, 1936.

Autopsy.—An inflammatory stenosis of the common duct was found at autopsy, with generalized peritonitis and obstructive icterus. There were no pulmonary changes of the type usually associated with asthma. Moderate chronic bronchitis, bronchopneumonia, and bronchiectasis were present as part of the terminal picture.

CASE 10.—A. A. K., a white male, aged forty-four years, was admitted to the University Hospital on June 16, 1935, complaining of shortness of breath and swelling of the legs and abdomen. Since the age of twenty-five years he had had attacks of wheezing, and dyspnea occurring chiefly in the spring and fall but initiated at any time by acute upper respiratory infections. The attacks were usually relieved by smoking stramonium leaf cigarettes. A continuous attack of expiratory dyspnea had been present for seven weeks previous to admission. The examination showed advanced glomerular nephritis, hypertension, bronchial asthma, and uremia. Differential blood smears showed a 3 per cent to 7 per cent eosinophilia. Death in uremic convulsions occurred on November 2, 1935.

Autopsy.—The chief findings at autopsy were subacute glomerular nephritis and cardiac enlargement with marked left ventricular hypertrophy. The lungs showed thickening of the basement membrane of occasional bronchi with moderate sac culation of the mucous gland ducts.

DISCUSSION OF GROUP II

Ten cases in which the clinical history, physical examination, and laboratory data answered the criteria of bronchial asthma have been presented. The ages in this group varied from eighteen years to seventy-nine years. The duration of the asthma varied from one year to forty-five years. The etiology of the asthma was known to be extrinsic proteins in five cases; the cause of the attacks were respiratory tract infections or was unknown in the other five cases. The causes of death are as listed in Table III. It is noteworthy that they do not show a preponderance of pulmonary disease.

None of these cases presented the complete pathologic picture described in Group I for status asthmaticus. Two of the cases (8, 9) failed to show any of the pulmonary changes; eight showed one change, that is hyaline thickening of the basement membrane. This thickening, most marked in the larger bronchi and trachea, was not regularly associated with a history of chronic upper respiratory infections or with pathologic evidence of chronic pulmonary suppuration. In two other cases there was, in addition, slight hypertrophy of the bronchial musculature, sacculation of the smaller bronchi, and slight peribronchial eosinophilia.

It would seem evident that a prolonged, intermittent asthma will not produce the full pathologic picture constantly seen in status asthmaticus. The one uniform pathologic finding in eight of the ten cases cannot be explained by chronic suppurative pulmonary disease. Whether it is a result of long standing asthma, and of asthma alone, or only an incidental finding remains a question.

In the study of Group III, which follows, an attempt was made to correlate the pathologic finding of hyaline thickening of the basement membrane with a clinical diagnosis of bronchial asthma.

TABLE III

SUMMARY OF GROUP II

CASE NUMBER	AGE	DURATION OF ASTHMA	MICROSCOPIC FINDINGS	CHRONIC PULMONARY PATHOLOGY	CAUSE OF DEATH
	yrs.	yrs.			
1	79	40	Slight hyaline thickening of basement membrane of large bronchi only. Slight peribronchial eosinophilia		Heart failure. Confluent broncho-pneumonia
2	62	20	Marked hyaline thickening of basement membrane in large bronchi		Pulmonary embolism. Broncho-pneumonia
3	50	45	Moderate hyaline thickening of basement membrane of medium-sized bronchi only	Chronic fibroid pneumonia	Cerebral hemorrhage. Pulmonary embolism and infarction
4	18	15	Hyaline thickening of large and small bronchi. Sacculation of bronchi and trachea	Many bronchiectatic abscesses	Broncho-pneumonia. Empyema
5	53	2	Slight hyaline thickening of basement membrane of large bronchi	Bronchiectasis	Cholecystitis. Peritonitis
6	51	35	Hyaline thickening of basement membrane of medium-sized bronchi only	Chronic fibroid pneumonia	Nephritis. Uremia
7	38	8	Slight hyaline thickening of basement membrane. Slight hypertrophy of bronchial musculature		Carcinoma of the cervix
8	47	25		Carcinoma, bronchitis	Carcinoma of lung
9	35	?			Stone in common bile duct. Broncho-pneumonia
10	44	19	Moderate sacculation of the mucous gland ducts. Thickening of basement membrane of occasional bronchi. Very slight peribronchial eosinophilia		Glomerular nephritis. Uremia

GROUP III

CASE 1.—S. M., a nine-year-old male, entered the University Hospital January 6, 1933, because of abdominal pain and distension of several months' duration. Acute upper respiratory infections with tonsillitis had been of frequent occurrence. There was no history of an allergic manifestation. The family history revealed

asthma in a paternal grandmother. The physical examination revealed an undernourished boy with a sallow complexion. The ribs were flared. The chest gave a dull percussion note at both bases. Fine râles were heard over the left base posteriorly. The abdomen was distended. A fluid wave and shifting dulness could be elicited. The spleen was felt five fingers breadths below the costal margin. The blood examination showed a severe secondary anemia. No eosinophils were seen in the (Wright) stained blood smears. The carbon-dioxide combining power was 19 volumes per cent, and the blood sugar was 33 mg. per 100 c.c. The disease was rapidly progressive, death occurring on Jan. 16, 1933. The clinical diagnosis was Banti's disease.

Autopsy.—Showed atrophic cirrhosis, ascites, and chronic passive congestion of the spleen. Grossly, the lungs showed no emphysema or mucous plugs. Microscopically, the basement membrane of the large bronchi was thickened. The heart was normal for the age.

CASE 2.—F. G. R., white male, aged forty-seven years, entered the otology service on May 19, 1931, because of a nasal obstruction and postnasal drip. Submucous resection and nasal polypectomy relieved his nasal symptoms. He returned to the hospital on November 3, 1932, complaining of weakness and painful swelling of the ankles. Further history gave information of a chronic productive cough benefited by postural drainage.

Examinations suggested the diagnosis of periarteritis nodosa, or a dermatoneuro angiomyositis; chronic bronchitis, and bronchiectasis. During his stay in the hospital he gradually became weaker, developed pneumonia, and died on January 31, 1937. The history and findings would exclude bronchial asthma.

Autopsy.—The pathologic diagnosis was periarteritis nodosa. Associated with this there was a marked eosinophilia. The lungs showed some of the changes seen in Group I. There was marked thickening of the basement membrane of the large and small bronchi, moderate sacculation of the bronchi, hypertrophy of the bronchial musculature and patchy eosinophilia. Grossly there was no emphysema, and no mucinous plugs were seen.

The heart showed a moderate enlargement, mitral vegetations, eospinophilic infiltrations about the arterioles, and many small healed and healing infarcts.

CASE 3.—J. C., a white male, of seventy years, was admitted to the genitourinary surgical service on October 20, 1931, because of lower abdominal pain and difficulty in urination. The findings were those of senility, arteriosclerotic heart disease with slight decompensation, a moderately enlarged prostate, and a distended bladder. On Dec. 1, 1931, he suddenly became comatose and died the following day. He had had hay fever during July and August for many years, but cough was the only respiratory symptom that had ever occurred.

Autopsy.—The prostate showed cystic glandular hyperplasia. Associated with this was a marked cystitis with ascending pyelitis. The heart was moderately hypertrophied. The basement membranes of many of the large bronchi showed a moderate thickening, with questionable hypertrophy of the bronchial musculature. There were slight peribronchial eosinophilic infiltrations.

CASE 4.—M. S., a white female, aged forty-one years, was admitted to the dermatological service on April 19, 1932, because of a dermatitis medicamentosa. The general examination revealed, in addition to the skin eruption, a far advanced medullary squamous cell carcinoma of the cervix. Death from bronchopneumonia occurred two days after her fourth admission (Jan. 30, 1933). There was nothing in the history or physical examination that would suggest bronchial asthma.

Autopsy.—At autopsy a far advanced medullary squamous cell carcinoma of the cervix with extensive metastases was found. The lungs showed grossly a mucopurulent exudate and microscopically there was an early bronchopneumonia. The basement membrane of the large bronchi showed a moderate thickening, occasionally associated with hypertrophy of the musculature. The heart was not enlarged, and the myocardium showed slight brown atrophy.

CASE 5.—A. W., a white female of twenty-eight years, was first seen at the University Hospital on December 23, 1932, because of headaches and fainting spells. Head colds occurred frequently during the winter months. Studies revealed a large temporosphenoidal astrocytoma. A large portion of the tumor was removed with considerable relief of symptoms. The patient returned to the hospital on May 5, 1934, because of a recurrence of her symptoms. She died four days later during a convulsive seizure. No personal, nor family history of allergic manifestations could be obtained.

Autopsy.—The autopsy revealed a recurrent brain tumor with an associated purulent encephalitis. In the lungs there was an insignificant hypertrophy of the bronchial musculature and moderate thickening of the basement membrane. There was a slight peribronchial eosinophilia. A few of the small and large bronchi were filled with mucin, although mucinous plugs were not noted grossly. The heart showed nothing abnormal.

CASE 6.—T. F., an eight-year-old male, entered the University Hospital on April 7, 1933, for tonsillectomy. Acute upper respiratory infections and sore throat had been of common occurrence. He had had several attacks of migratory joint pain.

Physical examination revealed rheumatic heart disease with gross cardiac enlargement. Mild decompensation was present. His course was rapidly downhill, death occurring in acute cardiac decompensation on June 8, 1933. There was no history of allergic disease in the patient or the patient's family. Repeated blood smear studies failed to reveal an abnormal number of eosinophiles.

Autopsy.—The pathologic diagnosis included rheumatic heart disease with right ventricular hypertrophy and ascites. The lungs showed marked passive congestion with brown induration. The basement membranes of the large bronchi were markedly thickened, there was moderate sacculation of some of the bronchi and occasionally mucin in the bronchi. There was a slight peribronchial eosinophilia.

CASE 7.—J. W., a white male of seventy-two years, was admitted to the surgical service on April 24, 1936, because of weakness and an epigastric mass.

The examinations showed a nodular enlargement of the stomach and a hypoplastic anemia. An exploratory laparotomy was performed on May 29, 1937. Death occurred on the same day. The history and physical examination failed to suggest the presence of bronchial asthma.

Autopsy.—This patient had a far advanced carcinoma of the stomach with multiple metastases. Bronchopneumonia was of moderate extent. Thickening of the basement membrane of the larger bronchi was well marked. The heart showed many old small infarcts with myocardial fibrosis.

CASE 8.—G. E. C., a white male aged sixty years, entered the University Hospital on Feb. 20, 1936, because of epigastric pain and vomiting.

The examinations revealed a large carcinoma of the lower half of the stomach, which was removed. The postoperative course was stormy, death occurring on April 2, 1936. There was nothing in the history or physical examination that would suggest bronchial asthma.

Autopsy.—The cause of death was a carcinoma of the stomach with local metastases and generalized peritonitis. In the lungs there was well marked thickening of the basement membrane of the large bronchi. Bronchopneumonia was of slight extent. There was no hypertrophy of the heart.

CASE 9.—G. E. M., a male, aged two years and eleven months, was entered in the pediatric service of the University Hospital on October 6, 1935, because of vomiting and labored respirations. He had been perfectly well all his life until thirty-six hours before admission to the hospital. The physical examination showed a semicomatose male child breathing rapidly and deeply. The lung fields were clear. The liver was palpable two fingers breadth below the right costal margin. The urinalysis showed the presence of sugar and acetone. The carbon dioxide combining power of the blood was 29 volumes per cent. The child went into a deep coma and expired eighteen hours after admission. There was no personal, or family history of allergic disturbances.

Autopsy.—At autopsy there was found an acute toxic parenchymatous degeneration of all organs. There was no pneumonia, only edema, congestion, and hemorrhage of the lungs. The large, and a few of the medium-sized, bronchi showed moderate thickening of their basement membranes. The heart was normal for the age.

CASE 10.—H. C. S., white male, aged seventy-eight years, was admitted to the surgical service of the University Hospital on October 9, 1936, because of vomiting, suprapubic pain, and dysuria.

Physical examination showed a mentally confused, emaciated, dehydrated, white male with a distended bladder and a grossly hypertrophied prostate. Death in severe kidney insufficiency occurred on October 10, 1936.

There was no history of asthma, nor other allergic manifestation in the patient, nor his family. Colds had been present most of his life, averaging about three attacks each year.

Autopsy.—The chief findings were cystic glandular hyperplasia of the prostate, chronic cystitis, and ascending ureteropyelitis. In the lungs there was a purulent bronchitis, a hypostatic lobular pneumonia, and emphysema without mucinous plugs. The trachea and large bronchi showed a slight thickening of their basement membranes. There was moderate hypertrophy of the left ventricle of the heart.

CASE 11.—K. K., a white male of forty-five, was admitted to the medical service of the University Hospital on May 16, 1933, because of weakness, dyspnea on exertion, and a marked pallor.

Examination revealed a pernicious anemia. An infection with the Welch bacillus developed in a decubital ulcer, from which the patient died on May 25, 1933. There was no suggestion of bronchial asthma from the history, or physical findings.

Autopsy.—Autopsy confirmed the pernicious anemia with central nervous system involvement. There was osteomyelitis with gas bacillus infection. The lungs showed no pneumonia and only localized edema. There was fairly marked hyaline thickening of the basement membrane of the large bronchi and a slight peribronchial eosinophilia.

The diagnosis of bronchial asthma in this group was made or suggested by the microscopical findings in the autopsy material. All cases in which the histories were inadequate were discarded. Eleven records were sufficiently complete to use in this study. None of these cases gave a history, or had physical findings, suggestive of bronchial asthma.

Therefore, on none of this group was this diagnosis made before death. The ages varied from two to seventy years, the average being fifty years. The causes of death were variable as listed in Table IV.

None showed the "complete pathology" associated with status asthmaticus as seen in Group I. All 11 showed a hyaline thickening of the basement membrane of the large bronchi and trachea in a varying degree. It was upon this pathologic change that asthma was suggested by the pathologist. The photomicrograph (Fig. 2) taken from case 5 demonstrates this change in a large bronchus, without the other changes shown in Fig. 1. Scattered additional findings were noted in some of the cases as shown in Table IV.

Fig. 2.—(Case 5), Section of large bronchus showing the hyaline thickening of the basement membrane (×90).

There was no constant association with chronic upper respiratory disease, nor was suppurative pulmonary disease a frequent cause of death.

The weakness of histories taken without the specific disease in mind is admitted, but we feel that these 11 cases had adequate investigation and none gave a history, nor had physical findings, or laboratory data indicative of bronchial asthma.

GENERAL DISCUSSION

In Group I the pathologic picture in patients dying in status asthmaticus was uniform and in accordance with the result of previous studies. This picture represents the fully developed pathology of

bronchial asthma, which would probably be found in any individual during the height of an attack. That the entire pathology of bronchial asthma may be of but temporary occurrence is well illustrated by Group II. All of these cases had intermittent asthma of prolonged duration, death occurring from some intercurrent disease. The pathologic pul-

TABLE IV

SUMMARY OF GROUP III

CASE NO.	AGE	PATHOLOGY	CHRONIC UPPER RESPIRATORY TRACT INFECTION	CAUSE OF DEATH
1	yrs. 9	Hyaline thickening of basement membrane of large bronchi	Frequent head colds	Atrophic cirrhosis of liver
2	47	Marked hyaline thickening of large bronchi and moderate hypertrophy of their musculature. Moderate sacculation of the large bronchi. Eosinophilic infiltration	Nasal polyps. Postnasal discharge. "Winter colds"	Angioneuromyositis. Periarteritis nodosa
3	70	Moderate hyaline thickening of basement membrane of large bronchi. Slight peribronchial eosinophilic infiltrations	No	Prostatic hypertrophy. Uremia
4	41	Moderate thickening of basement membrane of large bronchi. Moderate eosinophilia	No	Carcinoma of cervix. Bronchopneumonia
5	28	Moderate thickening of basement membrane and slight hypertrophy of bronchial musculature. Slight peribronchial eosinophilia	Head colds in the winter	Recurrent brain tumor
6	8	Marked hyaline thickening of basement membrane and moderate hypertrophy of musculature. Slight peribronchial eosinophilia	Many acute respiratory tract infections	Rheumatic heart disease
7	72	Moderate hyaline thickening of large bronchi only	No	Carcinoma of stomach
8	60	Well marked thickening of basement membrane in large bronchi	No	Carcinoma of stomach
9	3	Moderate hyaline thickening of large and small bronchi	No	Acidosis
10	78	Slight hyaline thickening of basement membrane of trachea and large bronchi	Many "colds"	Hypertrophy of prostate. Uremia
11	45	Moderate hyaline thickening of basement membrane of large bronchi. Slight evidence of hypertrophy of bronchial musculature. Slight peribronchial eosinophilia	No	Pernicious anemia. Osteomyelitis

monary findings were never in toto those of status asthmaticus. The one constant indication of previous asthma that was found in the lungs was the hyaline thickening of the basement membrane. This was present in eight of the ten cases of Group II. However, when hyaline thickening of the basement membrane was used for the diagnosis of previous asthma, clinical studies failed to corroborate the diagnosis of asthma. It, therefore, becomes increasingly evident that asthma does not leave permanent pathologic changes in the lungs that might be used for diagnostic purposes, and on the other hand hyaline thickening of the basement membrane alone, is not a certain indication of clinical bronchial asthma.

CONCLUSIONS

1. A group of seven cases in which death may be attributed to asphyxia during status asthmaticus is reported.

2. The records in ten cases that had the necessary clinical criteria of asthma but in which death occurred from other intercurrent disease have been reviewed as to the gross and microscopic findings of the autopsies.

3. Eleven cases in which the microscopic examination of the autopsy material suggested bronchial asthma were reviewed in regard to their clinical history of asthma.

4. A pathologic diagnosis of bronchial asthma can be made only when the majority of the following criteria are present: (A) Hyaline thickening of the basement membrane of medium sized bronchi; (B) hypertrophy of the musculature of medium sized bronchi; (C) mucinous plugs in large and small bronchi; (D) eosinophilic infiltrations; (E) sacculation of the bronchi; and (F) excessive production of mucin and widening of the mouths of the bronchial glands.

5. Morphine and atropine should never be used in the management of cases of status asthmaticus.

6. Bronchial asthma may occur without leaving permanent pathognomonic pathologic changes.

REFERENCES

1. Macdonald, I. G.: Local and Constitutional Pathology of Bronchial Asthma, Ann. Int. Med. **6**: 253, 1932.
2. Waldbott, G. L.: Pathologic Changes in Asthmatic Infants, Am. J. Dis. Child. **49**: 1531, 1935.
3. Waldbott, G. L.: Comparison of Pathological Changes of Infantile Asthma with Asthma of Long Duration, J. ALLERGY **7**: 264, 1936.
4. Bubert, H. M., and Warner, C. G.: Fatal Asthma, J. A. M. A. **104**: 1469, 1935.
5. Michael, P. P., and Rowe, A. H.: Pathology of Two Fatal Cases of Bronchial Asthma, J. ALLERGY **6**: 150, 1935.
6. Hansen, O. S.: Death From Asthma, Minnesota Med. **19**: 445, 1936.
7. Brulé, M., Hillemand, P., Delarue, J., and Netter, A.: Un nouveau cas de mort au cours d'une crise d'asthme, étude anatomophysiologique, Bull. et mém. Soc. méd. d. hôp. de Paris **51**: 981, 1935.
8. Antoniazzi, E.: Fatal Case of Bronchial Asthma; Autopsy Report, Policlinico (sez. med.) **40**: 345, 1933.
9. Riopelle, J. L.: Un nouveau cas d'asthme mortel avec autopsie, Ann. d'anat. path. **10**: 1179, 1933.

10. Wilmer, H. B., Eiman, J., and Miller, M. M.: Pathologic Picture in a Case of Essential Bronchial Asthma—Roentgen Findings Ante and Post Mortem, J. ALLERGY **7**: 156, 1936.
11. Colton, W. A., and Ziskin, T.: The Heart in Bronchial Asthma; Report of Nine Cases in Which Bronchial Asthma Was the Cause of Death, M. Bull. Vet. Admin. **13**: 117, 1936.
12. Funk, V. K., and Higgins, G. K.: Bronchial Asthma—Case Report, Minnesota Med. **19**: 460, 1936.
13. Rackemann, F. M.: Fatal Asthma; Report of a Case With Autopsy, Boston M. & S. J. **194**: 531, 1926.
14. Coca, A., and others: Asthma and Hay Fever in Theory and Practice. Part 2, Asthma by Matthew Walzer, Springfield, Ill., 1931, C. C. Thomas.
15. Huber, H. L., and Koessler, K. K.: Pathology of Asthma, Arch. Int. Med. **30**: 689, 1922.
16. Kountz, W. B., and Alexander, H. L.: Death from Bronchial Asthma; Report of Three Cases, Arch. Path. **5**: 1003, 1928.
17. Alexander, H. L., Luten, D., and Kountz, W. B.: Effects on Heart of Long-standing Bronchial Asthma, J. A. M. A. **88**: 882, 1927.
18. Paul, W. D.: The Heart in Bronchial Asthma, J. Iowa M. Soc. **25**: 643, 1935.

DISCUSSION

DR. KARL D. FIGLEY, Toledo, Ohio.—I think it is not necessary for me to stress the fact that this is a very important contribution to the literature on the pathology of bronchial asthma. We are all of us in search for some objective findings with regard to what is the allergic constitution. I do not know that Dr. Sheldon has been able to identify or isolate this allergic constitution, but I trust that in his summation he will dilate somewhat upon the thymicolymphatic findings in these cases. Pathologic findings in uncomplicated asthma are those resulting from an immunologic reaction. In the early stages, this reaction is reversible, but as there are succeeding attacks of asthma, these tissue reactions become irreversible. Consequently, one cannot expect to find such marked pathologic changes in bronchial asthma as occur in diseases accompanied by tissue destruction, such as many of the infections.

Not being a pathologist, I do not feel qualified to further discuss this very valuable contribution. In closing, I simply want to thank Dr. Sheldon for bringing up this subject and presenting in such a very beautiful manner the findings which he has done.

DR. GEORGE L. WALDBOTT, Detroit.—I, too, had the privilege of a preliminary reading of this interesting paper and was also impressed with the thoroughness and excellence of its presentation. I observed that the authors did not corroborate the pulmonary findings of edematous hemorrhagic areas which I described a few years ago and which were recently confirmed by G. Waaler of Stockholm.* I presume, however, that the absence of these findings is due to the fact that the asthma had been present for 13 months. Had this case come to autopsy within the first few weeks of the onset of the asthma, the lesions would probably have been present.

DR. ROBERT WARD LAMSON, Los Angeles.—I concur heartily in most of the things that Dr. Sheldon has brought out. It should be noted that these differ somewhat from some of Dr. Macdonald's earlier concepts. Dr. Butt and myself admit our indebtedness to Dr. Macdonald for many suggestions during the early part of our study. Pathologists and

*Localization of Allergic Inflammation. Acta path. et microbiol. Scandinav., supp. 26, pp. 227, 1936.

clinicians, of course, tend to have independent views on any subject. Many pathologists have thought that they had absolute criteria of bronchial or allergic asthma. We clinicians felt that they did not. After many heated arguments between myself and members of the department of pathology, it was finally concluded that we would keep an open mind and try to find out what could be put together from the clinical and pathologic standpoints to establish these criteria. So far, we have found essentially what Dr. Sheldon has, that there is nothing pathognomonic of asthma. Of course, it would be a little late to help the patient, even if we did discover an absolute criterion.

One always has hopes that by looking at a case in retrospect, he might be able to anticipate and perhaps do something for another patient during life. Our discussions and observation have stimulated Dr. Butt and other members of the department of pathology to carry on a study of the broader problem of lung pathology in general. We find that one can take the lung of a patient dying of almost any ailment and by picking out isolated areas find many of these supposedly typical pictures of asthma. For example, a Mexican child of some ten or eleven years of age died in the Santa Fe Hospital last summer. No history could be obtained of any attack of paroxysmal dyspnea. A postmortem examination of the lungs by Dr. Butt revealed pathology almost as characteristic of asthma as has been shown in the first seven cases today; thus we suspect that much of this lung picture is produced in individuals dying of conditions other than asthma. I believe some of Dr. Sheldon's observations support such a thesis. Since the pathology of asthma is still a moot question, contributions such as presented by Drs. Thieme and Sheldon today are of great value. Our own series represents patients from the other end of the country. Racial, age, economic, and other differences are inevitable. Do these have any relationship to clinical or pathologic factors?

I would like to ask Dr. Sheldon if he has any impression as to about how long it takes to produce the changes he indicated. We were struck by the life insurance company's contention that asthma is a great hazard to life. Our series did not bear out this assumption. We did somewhat as Dr. Sheldon has, that is, emphasized the duration of symptoms. We cannot show that the pathology goes parallel with this factor. A patient with long duration might show less pathology than one with a few weeks of dyspnea. We are carrying out a companion study of some 500 x-ray examinations; many of which represent the cases reported in our article. We have not, as yet, completed the study, but thus far we cannot determine from the x-ray examination the individual who is ultimately going to succumb to (or because of, or with) asthma.

Dr. Sheldon has been very timely in emphasizing a point which has not often been brought out in previous literature, namely, the difference between dying of asthma and with asthma. I want to congratulate him and his collaborator on this excellent paper.

DR. HARRY L. HUBER, Chicago.—You gave periarteritis nodosa as the cause of death in one of your cases of bronchial asthma. Did you find any evidence of this in your other cases? Dr. Milton Cohen, Dr. Jaffee, and others have shown that, pathologically, periarteritis nodosa should be classed as an allergic disorder.

DR. JOSEPH HARKAVY, New York.—In one of two cases of fatal bronchial asthma which I reported in 1930, I described eosinophilic infiltrations in a certain number of branches of the pulmonary arteries. I suspected then that the pulmonary blood vessels in our patients' lungs, just as in the rabbit or guinea pig, were probably one of the sites of the allergic reaction. This patient also had an extremely marked hypertrophy of the right ventricle, so much so that it occupied the entire interspace between the right and left lungs.

On several occasions when papers on the pathology of bronchial asthma were presented before this Society, there was always a discussion as to whether the heart was enlarged or not, and there is still a constant controversy on this subject in the literature. It seems to me that in making up our minds as to whether the heart is enlarged or is not enlarged in bronchial asthma, we have to take a number of facts into consideration. First, the age of the patient at the time of death, whether or not he had hypertension, or any other organic disease which would be responsible for enlargement of the heart per se; second, did the patient, organically sound, die in a sudden acute attack of asthma induced by drugs or serums to which he was sensitive; third, did the patient have a chronic bronchial asthma with a superimposed emphysema, arteriosclerosis of the pulmonary vessels with increased tension of the lesser circulation leading to a right-sided cardiac hypertrophy; fourth, whether the patient had a bacterial asthma due to a chronic pulmonary infection, such as unresolved pneumonia or bronchiectasis, with a compensatory emphysema responsible for obliteration of the capillary blood vessels of the lungs and a secondary cardiac hypertrophy. Only when you take into consideration these various factors, can you interpret autopsy findings intelligently and express an opinion as to the relationship between the bronchial asthma of a given case and the presence or absence of hypertrophy of the heart.

Obviously children dying suddenly of an acute anaphylactic-like asthma will not have any cardiac enlargement, nor will allergic patients who get an overdose of antigen to which they are susceptible. I have seen patients admitted to the hospital suffering from recurrent pollen bronchial asthma, die suddenly after a dose of morphine administered for the purpose of controlling their paroxysm by a physician who never suspected that in addition to the pollen they might also be sensitive to morphine. At autopsy no hypertrophy of the heart was found. Postmortem study of such patients without a comprehensive realization of all the facts would lead the casual investigator to conclude that death from bronchial asthma is not associated with cardiac hypertrophy.

Thus the pathology of bronchial asthma becomes extremely complicated and it is impossible, as has been mentioned by Dr. Figley and Dr. Sheldon, to say that any one picture dominates the findings in this syndrome-complex. Autopsy reveals end results which must be interpreted in terms of the individuals disease patterns.

DR. SHELDON.—Dr. Figley asked about the thymicolymphatic constitution. It is my belief that this is a group of findings that differentiates or subdivides people into certain very definite groups. It is characterized, as you know, by abundant thymic remains, hypoplasia of the aorta, adrenals and myocardium, and generalized lymphoid hyperplasia. We do not mean to infer that the thymicolymphatic constitution is the answer to all asthma. We do mean to state that in the group of patients

that we have reported the vast majority of them fall into this group or this type of patient. Therefore, it seems to us that on the law of chance, if one does not belong to the thymicolymphatic constitution, the chance of having asthma is not as great as if you do belong to it.

In answer to Dr. Waldbott's discussion, I wish to again emphasize the point that the case aged eighteen months that we report had asthma of some duration. I merely mentioned this case because there was a discrepancy in the findings between his cases and ours.

In regard to Dr. Lamson's question concerning the duration of asthma in order to produce pathologic findings, it is my belief that asthma of very short duration may produce all of the findings. I also believe that in a very short time all the findings may subside and leave no evidence of their occurrence.

Dr. Huber asked about periarteritis nodosa. We had ample opportunity to study this particular patient. She came to the hospital several days before death occurred. Allergic investigative study was done, which was entirely negative. She was running a febrile course at the time she was investigated and that may have some bearing upon her negative findings. I am not capable of discussing periarteritis nodosa in its entirety at this time.

I am very happy that Dr. Harkavy brought up the discussion concerning the heart. I wish to reemphasize the point that in our series of 7 cases dying an asphyxia death during an asthmatic paroxysm none of them showed a right ventricular hypertrophy. I am aware that some of the cases that are reported had right ventricular hypertrophy. However, the exact cause of the ventricular hypertrophy reported is questionable, probably due to causes other than asthma.

One point that I wish to reemphasize is that hyaline thickening of the basement membrane is not pathognomonic of bronchial asthma. Most pathologists agree that the basement membrane becomes more prominent and hyalinized as an aging process. There are many additional causes of hyaline thickening other than asthma.

PREVENTION OF DERMATITIS VENENATA DUE TO POISON IVY IN CHILDREN*

A Comparison of the Value of the Single and Multiple Injection Methods

Matthew Molitch, M.D., Philadelphia, Pa., and
Samuel Poliakoff, B.Sc., Jamesburg, N. J.

WE have shown[1] that a weekly injection of an aqueous dilution of an alcoholic extract (1:50) of the poison ivy plant, given throughout the five months of the poison ivy season, will produce a 100 per cent immunity for that season. No reactions or pain were complained of, but a slight itching for about an hour at the site of injection was experienced by many. In order to get away from giving so many injections, we obtained a supply of extract from two different manufactures† who claimed satisfactory results for the entire season from one and two injections. Blank and Coca[2] using one of these extracts obtained immunity in from eighty to ninety-three per cent of their subjects, depending on the dose used. Gowen[3] used the same extract in seven patients who already had the dermatitis and in one for prophylactic purposes. These patients were all benefited and in addition became immune for the remainder of the season.

At the beginning of the poison ivy season, we found that we had 74 boys who gave a history of having had poison ivy before. We have found[1] that the history of a previous attack is almost as reliable as patch tests. Our subjects were all inmates of the New Jersey State Home for Boys and ranged in age between twelve and seventeen years. The institution is located in an area in which the poison ivy plant is abundant. Most of the inmates work out in the open and for a week they take frequent hikes as part of their boy scout program. These boys were divided approximately in three groups, and the one selected for immunization were those who would most probably remain in the institution over the summer. Twenty-eight boys were given two doses of one c.c. each of commercial product No. 1, two weeks apart. This extract is in an almond oil menstruum containing 10 per cent by volume of acetone and 0.1 per cent of solids, extracted from poison ivy leaves with acetone and freed from chlorophyl. Twenty-two boys were given a single 1 c.c. injection of commercial product No. 2. This extract is also in an almond oil menstruum and contains 15 per cent of solid extract of poison ivy leaves.

*From the School of Medicine, University of Pennsylvania, and the New Jersey State Home for Boys at Jamesburg.

†We wish to thank Lederle Laboratories, Inc., Parke Davis and Co., and E. R. Squibb & Sons for supplying the materials for this research.

Table I gives the results of our research. The injections were given during the early part of May, and the boys were observed until the latter part of August. Actually 46 boys developed poison ivy dermatitis, but only seven of them had been given the immunization treatments. The remaining 39 boys consisted of 15 who were in the institution at the time the experiment started, while the rest were either new arrivals

TABLE I

RESULTS OF IMMUNIZATIONS WITH EXTRACTS OF POISON IVY LEAVES

PREPARATION USED	NUMBER OF BOYS	RESULTS			
		DEVELOPED POISON IVY		DID NOT DEVELOP POISON IVY	
		NUMBER	PERCENTAGE	NUMBER	PERCENTAGE
Control*	15	6	40	9	60
Commercial product No. 1	28	3	10.7	25	89.3
Commercial product No. 2	22	4	18.2	18	81.8
Commercial product No. 3†	40	0	0	40	100

*We originally had 24 controls but nine left the institution in less than one month after the research was started. In addition, 33 boys developed "poison ivy" who were not originally in the control group, and who either never had had poison ivy before or who arrived in the institution after the research was started.

†The research with commercial product No. 3 was done two years ago and at that time 53 children, who had not been immunized, developed poison ivy.

or those with a negative history of sensitivity. It is seen from the table that the one injection and two injections methods give an immunity from 82 to almost 90 per cent.

Of the three failures in the group treated with commercial product No. 1, one boy developed his dermatitis twenty-four days after the first injection, or ten days after the second injection. The second and third boys both developed their dermatitis on the thirty-fifth day after the first injection, or twenty-one days after the second injection. No new cases appeared after the thirty-fifth day after the first injections. Blank and Coca[2] found that all of their failures occurred during the first six weeks, but they were reluctant to claim complete protection after that period as they had too few uninjected controls. The four failures in the group treated with commercial product No. 2 occurred respectively on the eighth, thirteenth, nineteenth, and eighty-fourth day after the single injection. It may be that an additional injection might have given even a higher percentage of success.

The practitioner, therefore, has at his disposal three methods for immunization; the weekly injections of an aqueous dilution of an alcoholic extract, or one of the two methods used in this research. I believe the patient should be given his choice, as it means either one, two, or twenty injections with excellent results varying between 82 and 100 per cent. The oil injections containing the extract were given intramuscularly, and the site was immediately sealed with adhesive. Eight boys within a few days developed a small area of dermatitis near the

site of injection. It may be that if collodion were used to seal off the site we might have eliminated this complication. None of the boys complained of pain and no systemic reactions were seen.

SUMMARY AND CONCLUSIONS

Twenty-eight boys were given two injections and 22 boys were given one injection of extracts of poison ivy leaves made by different manufacturers. Of these 50 boys, seven developed poison ivy dermatitis during the season. Thirty-nine children who were not immunized developed poison ivy dermatitis.

REFERENCES

1. Molitch, M., and Poliakoff, S.: Prevention of Dermatitis Due to Poison Ivy in Children, Arch. Dermat. & Syph. **33**: 725, 1936.
2. Blank, J. M., and Coca, A. F.: Study of the Prophylactic Action of an Extract of Poison Ivy in the Control of Rhus Dermatitis, J. ALLERGY **7**: 552, 1936.
3. Gowen, H. G.: Treatment and Prevention of Rhus Toxicodendron Poisoning, J. ALLERGY **4**: 519, 1933.

Special Report

THE HOUSE FLY AS A CAUSE OF NASAL ALLERGY

HEBER C. JAMIESON, M.B. (CAN.), EDMONTON, ALBERTA

IT HAS been shown by Parlato[1] that the caddis fly, butterfly, and moth are causes of nasal allergy. The house fly, Musca domestica, has been thought incapable of producing this, but the following case demonstrates the contrary.

CASE REPORT

R. H. P., female, aged forty-nine years, has had pollen allergy for fourteen years from mid-summer until frost. Asthmatic attacks occurred at times during this period. Recently she noticed that rhinorrhea and asthma came on while baking, and also that house flies buzzing about her face gave her violent fits of sneezing, and that her nose ran so much that she was in the habit of carrying a fly swatter in her hand during the fly season. Eating of much starchy food and sugar during the hay fever season increased the intensity of the pollinosis. House dust also caused sneezing.

The patient spent one year in a Rocky Mountain town at an elevation of 4,500 feet and had no hay fever or asthma. She gave a history of eczema on the neck and behind the ears for several weeks at the age of twenty-one, and hives at intervals from childhood. There was no family history of allergy.

Scratch tests were performed and reactions to Russian pig weed and sage, two weeds common in the locality where she lived, were obtained. Intracutaneous tests showed a marked reaction to wheat flour extract and a moderate response to city house dust, farm house dust, potato, and cocoa.

The house fly was disregarded until the patient requested that it be tested. Accordingly, a fly's wing was rubbed into a scratch with decinormal sodium hydroxide. In fifteen minutes there was a marked reaction. Several hours later the patient telephoned from her home to say that her arm was greatly swollen and that there was a red inflamed area an inch and a half by two inches in extent where the fly's wing had been tested.

A similar marked reaction occurred on retesting. Pyrethrum gave a negative result. An attempt was made to passively transfer, by sensitizing the skin of a nonallergic individual with defibrinated blood passed through a Berkefeld filter. The extract used was made by placing twelve small wings in 0.5 c.c. of buffered saline and allowing them to stand forty-eight hours. An intracutaneous injection of 0.1 c.c. of this extract was made on one of the prepared sites and on normal skin two days after the sensitizing injection. The result was questionable. However, on repeating the experiment ten days later on another sensitized site, a marked reaction occurred, as a red swollen area 2.5 cm. in diameter appeared in three hours. The site remained red, swollen, and tender for twenty-four hours. The control site was negative. This test was repeated on two subsequent occasions with similar results.

A very small fragment of a fly's wing was placed on the conjunctival border of the outer angle of the eye and left for thirty seconds. In a few minutes the

patient complained of smarting at the site of the application. In fifteen minutes there was a slight swelling of the lower lid and definite injection of the corneal vessels at the outer canthus.

Half a wing brushed inside one nostril caused sneezing at once and rhinorrhea within a few minutes. In this instance one could not rule out stimulation of the fifth nerve by the procedure, but the result was suggestive in view of the other positive tests.

A number of nonallergic individuals were found to give negative results to direct skin tests as well as to conjunctival and nasal tests.

The wing of the house fly is composed largely of chitin which is colorless, nitrogenous polysaccharide. Microscopically many spikes can be observed on its surface. There are no scales such as one finds on that of the caddis fly, butterfly, or moth.

SUMMARY

It is evident from the history, the positive scratch, intracutaneous, and passive transfer tests, that, although uncommon, the house fly can cause nasal allergy.

REFERENCES

1. Parlato, S. J.: Emanations of Flies as Exciting Causes of Allergic Coryza and Asthma; Hypersensitiveness to Moths and Butterflies, J. ALLERGY 3: 126, 1932.
2. Parlato, S. J.: Emanations of Flies as Exciting Causes of Allergic Coryza and Asthma; A Study of the Atopic Reagins of the Caddis Fly, Butterfly, and Moth, J. ALLERGY 3: 459, 1932.

Society Proceedings

THE ASSOCIATION FOR THE STUDY OF ALLERGY

ATLANTIC CITY, N. J., JUNE 7, 1937

Tobacco Sensitization in Rats.* JOSEPH HARKAVY, M.D., New York City. (Abstract.)

IN APRIL 1937, a preliminary report was made on the occurrence of tobacco sensitization in rats.[1] In the course of sensitization by the intraperitoneal injection of denicotinized tobacco, these rats developed gangrenous lesions of the toes previously described by Friedlander, Silbert, and Laskey[2] in 68 per cent of their male rats injected with an extract of Sano tobacco which had 60 per cent of the nicotine removed. In our experiments, however, a pooled denicotinized extract composed of Burley, Maryland, Virginia, and Xanthis tobaccos containing 0.085 mg. N. per cubic centimeter, was employed. Individual preparations of these same tobaccos had been used by us in demonstrating clinical hypersensitiveness to tobacco in vascular disease such as thrombo-angiitis obliterans, migrating phlebitis, and in angina pectoris associated with coronary artery disease.[3, 4]

The present communication is a summary of results thus far obtained in our immunologic studies on 22 animals, 15 of which were injected with the pooled tobacco extract, and 7 controls. The method of preparing the tobacco antigen has been described in previous publications.[3] The animals were injected with 0.1 c.c. of the tobacco extract intraperitoneally every day for six to twelve weeks, within which period a certain proportion of them developed gangrene of the toes. In order to elucidate the nature of these lesions, it was deemed necessary to determine whether the tissues of the injected animals had been sensitized to tobacco. It was obviously also important to ascertain whether the rats which had not developed gangrene had likewise become sensitized by this method of injection.

The question of sensitization was investigated by the utilization of the Schultz-Dale technique. The intestinal strip of the males and uterus of the female rats were used as the test objects.

Of the 15 injected rats, 12 were males and 3 females. The 7 controls consisted of 6 males and 1 female. One of the male control rats was

*From the Laboratories of Mount Sinai Hospital.

injected with 0.1 c.c. of ragweed pollen extract containing 0.1 mg. N. per cubic centimeter daily for ten weeks. The other 6 were normal.

The six noninjected control rats were used to learn the effect of various amounts of tobacco extracts on the excised intestinal strip and uterus of normal animals, and at the same time to titrate the optimal amount of tobacco which we could employ in studying the reactions of tissues obtained from the treated animals.

The 15 injected rats were prepared as follows: Nine rats, six males and three females received daily injection of tobacco only. Four male rats received 0.1 c.c. of a mixture consisting of tobacco plus horse serum and egg white or ragweed, daily. One male rat received 0.1 c.c. of a mixture of tobacco extract plus meningococcus toxin, daily. One male rat was injected with nicotine tartrate 1:10,000 in sublethal doses for eight months.

Of the 11 male rats injected with tobacco, 5 or 55 per cent had developed gangrene of the toes. Each of these 5 male rats with toe lesions showed clear-cut evidence of having been sensitized to tobacco by contraction of the intestinal strip suspended in Tyrode's solution when tobacco extract was added to the bath. Although 4 of these 5 male rats had been simultaneously injected with either horse serum, egg white, or ragweed in addition to tobacco, no evidence of sensitization to these other antigens could be demonstrated.

None of the remaining 6 male rats, 5 of which had been injected with tobacco only and one with tobacco plus meningococcus toxin, developed gangrene of the toes. Only 3 of the 6 showed evidence of sensitization to tobacco as determined by the intestinal strip. The other 3 were negative. The 3 positively reacting rats consisted of one injected with Sano tobacco for eight months in 1935 and tested one year after injections were stopped; one injected for twelve weeks; and one injected eight months with Sano tobacco, thyroidectomized and four months later reinjected again with tobacco.

The male rat, injected with nicotine only, showed no evidence of sensitization to nicotine or to the tobacco extract.

Of the three female rats injected with tobacco only, not a single one developed gangrene and none of them gave any evidence of tobacco sensitization either in the intestinal strip or uterus.

None of the intestinal strips of the 7 control rats including the one injected with ragweed only showed any reaction to tobacco extract when tested with doses as high as 1.6 c.c. The titrated doses of tobacco used in testing the sensitized intestinal strip in this group of animals varied from 0.2 c.c. to 0.5 c.c.

No evidence of sensitization to ragweed was obtained in the ragweed injected rat.

SUMMARY

1. Five male rats injected with tobacco extracts who developed gangrene of the toes were sensitized to tobacco.

2. Of 6 male rats injected with tobacco who did not develop gangrenous lesions of the toes only three showed tobacco sensitization.

3. In 4 rats who in addition to tobacco were injected with horse dander, egg white or ragweed, no evidence of sensitization to any of these substances could be demonstrated.

4. None of the 3 female rats injected with tobacco developed gangrene of toes, and no evidence of tobacco sensitization could be obtained.

I wish to acknowledge my appreciation to George Brooks, B.S., for his assistance in carrying out these experiments.

REFERENCES

1. Harkavy, Joseph: Tobacco Sensitization in Rats, Proc. Soc. Exper. Biol. & Med. **36:** 381, 1937.
2. Friedlander, M., Silbert, S., and Laskey, N.: Toe Lesions Following Tobacco Injection in Rats, Proc. Soc. Exper. Biol. & Med. **34:** 156, 1936.
3. Harkavy, J.: Tobacco Sensitiveness in Angina Pectoris and Coronary Artery Disease, Proc. Soc. Exper. Biol. & Med. **30:** 683, 1933.
4. Harkavy, J.: Skin Reactions to Tobacco Antigen in Smokers and Nonsmokers, J. ALLERGY **5:** 131, 1934.

DISCUSSION

DR. MARION B. SULZBERGER, New York.—First, I would like to compliment Dr. Harkavy and also Dr. Silbert and Dr. Friedlander and their coworkers on the work which Dr. Harkavy mentioned. You are all aware of the fact that for a long time tobacco has been clinically incriminated in certain diseases of the blood vessels; that there is adequate evidence, for instance in thrombo-angiitis obliterans, that the use and abuse of tobacco is a very important factor in the prolongation and the exacerbations of the disease. You are also aware that some years ago both Dr. Harkavy and I, approximately simultaneously and independently, had the idea that because of the peculiar variability in the individual susceptibility to tobacco effects, and because of a mass of other evidence, the ill effects might be due not to the nicotine content, not to the alkaloid content, and not to the poisonous combustion products of tobacco, but due rather to the fact that tobacco is a plant; and that like certain other plants tobacco might sensitize and act as an allergen rather than as a toxicologic or intrinsically poisonous substance.

After Dr. Harkavy and I had given birth to this hypothesis, we adduced some experimental evidence to support it; perhaps even sufficient evidence to justify the dignification of our "hypothesis" by the term of "theory." That evidence consisted in my work of proving that smokers gave a much higher percentage of positive skin test reactions to denicotinized tobacco extracts than did nonsmokers; furthermore, Dr. Harkavy's figures and in combination with mine showed fairly conclusively that in thrombo-angiitis obliterans there was even a higher percentage of immediate skin reactions, wheal and flare reactions to tobacco than in normal smokers.

This child of ours was immediately attacked and there appeared strong antagonists to the theory that tobacco acted as a sensitizer, as an allergen in the production of certain vascular diseases. I have been afraid for a long time that perhaps because this theory was, so to say, one of my children, I might have been prejudiced in its favor, a prejudice not unusual on the part of a parent. However, I now believe that if Dr. Harkavy's work of today is confirmed, this theory child will survive and grow up. I think that the work reported today, in conjunction with Silbert's and Friedlander's previous findings, adds not inconsiderable support to the theory of the importance of the allergenic properties of tobacco in the production of certain diseases.

If I may recapitulate some of the evidence supporting this theory as applied to thrombo-angiitis obliterans, I should do so as follows: In the first place, this disease is one in which the clinical evidence is the strongest as to the rôle of tobacco; second, if Dr. Harkavy's results (and my own on a few cases) are correct, then it is shown that thrombo-angiitis patients give positive skin test reactions to the incriminated substance in a higher percentage than does any other group of individuals. Third, exposure to approximately the same quantity of tobacco does little, if any, harm to some individuals while it proves harmful out of all proportion to a very few especially sensitive or predisposed persons. In discussing this and other points in evidence some years ago and in closing two of my early papers on the subject of tobacco as an allergen, I said as follows: "It is hoped that the new immunologic approach and the employment of animal sensitizations will lead to the experimental reproduction of certain diseases clinically attributable to damage by tobacco. As is well known, all toxicologic attempts to do this have failed"[1] and "In the case of some vascular diseases of tobacco hypersensitivity, I believe that the new approach has already taught us that it is probably more correct to speak of tobacco as the 'noxious weed' than to refer to it as 'my Lady Nicotine.' "[2]

In Dr. Harkavy's work we have evidence that my statements were not too far fetched. For he has, to my knowledge for the first time in medical history, sensitized animals to tobacco extracts containing negligible quantities of nicotine; and in these very animals vascular lesions are produced, which grossly at least, resemble those of a human disease in which exposure to tobacco plays an important rôle.

REFERENCES

1. Sulzberger, M. B.: Recent Immunologic Studies in Hypersensitivity to Tobacco, J. A. M. A. **102**: 11, 1934.
2. Idem: Recent Immunologic Experiments in Tobacco Hypersensitivity, Bull. New York Acad. Med. **9**: 294, 1933.

DR. HARRY L. ALEXANDER, St. Louis.—This is very important work and so we must be careful. I would not presume to deny that this lesion in the foot is due to sensitization, but I think we must be very careful in interpreting the fact that one gets constriction of the bowel which indicates that that organ is sensitive as meaning that this vascular lesion is the same mechanism.

I think it would be interesting to examine pathologic sections of the vascular structures instead. In order to get gangrene, one presumably

gets endothelial proliferation or an inflammatory process. If this be allergic, it is quite a different pathologic mechanism than operates in causing bowel contraction.

There are ways of testing vascular structures, taking vascular rings and seeing if they are sensitive, by merely putting them in vitro in baths and there are ways of registering vascular pressures in vivo.

I think really before one can assume this is truly sensitization, the emphasis should be on the lesions in the vascular structures and not necessarily on the bowel.

Dr. M. Murray Peshkin, New York.—Dr. Harkavy should be congratulated for proving by animal experimentation that tobacco contains a protein substance which is an active specific anaphylactic antigen. My interest in tobacco has finally been aroused by Dr. Harkavy. Dr. Landay and I tested over 150 children. They were tested several years ago and many of them retested last year against extremely potent tobacco extracts which Dr. Harkavy kindly supplied. We were impressed with the fact that many reactions to tobacco were obtained in children of all ages, male as well as female.

We were further impressed with the fact that in many of these children positive reactions to tobacco were obtained only by the intradermal technique. Tobacco, like house dust, does not readily lend itself to showing positive reactions by the scratch method no matter how high a concentration of the extract is used. We also confirmed the findings Dr. Harkavy reported several years ago that a large percentage of patients who are positive to pollen, either timothy or ragweed, also show a positive reaction to tobacco.

Passive transfer tests for tobacco were performed with the serums from about 75 children. We were surprised to find that positive passive transfer reactions were obtained with the serum from most children who showed a positive reaction to tobacco by the intradermal test.

These findings are in the nature of a preliminary report because we have not submitted them for publication as yet. It is certain that tobacco sensitivity by test does exist in children of all ages and that positive transfer reactions are obtained in a large number of these children. What significance tobacco sensitivity has in children cannot be stated at this time.

Dr. Harkavy.—In formulating a theory about a disease, it is obviously necessary to supplement clinical observations by experimental evidence in order to prove the theory. In working out the idea of tobacco sensitization in vascular disease which I first presented in 1932, I have attempted to follow the postulates of Koch in establishing the etiology in a disease-complex.

A great many difficulties presented themselves in this investigation, and I have no illusions as regards today's contribution being final. I realize that there are many phases that still have to be elucidated before the mechanism involved in tobacco sensitization of the cardiovascular system is clear.

My results thus far show unequivocally that a certain number of tobacco injected rats develop gangrene of the toes. There is very little

question but that the gangrene indicates death of tissue. Necrosis of tissue implies cessation of blood flow which in turn is dependent upon occlusion of blood vessels.

When Friedlander and Silbert reported their work on the production of gangrene of the toes in tobacco injected rats at the New York Academy of Medicine, the first thing I thought of was that the lesion might represent an Arthus phenomenon. I asked Dr. Opie, who presided, whether he thought so too. He was noncommittal. It seems to me, if this were an Arthus phenomenon, then by analogy, vascular thrombosis which is a prominent feature in the necrosis associated with the Arthus lesion might likewise play a rôle in the production of the changes in the toes of our sensitized rats. Histologic preparations, however, of some of the involved toes have up to the present revealed only a rare thrombosis of the smaller vessels of the affected part. The essential finding noted by Dr. Henry Horn, working with me, has been an inflammatory reaction of nonspecific nature within the soft parts. This process precedes the gangrene which has been observed in the experimental animals.

In answer to Dr. Alexander's argument about proving the existence of sensitization of the blood vessels directly, I wish to state that I am fully aware of this possibility experimentally. Koessler, a number of years ago, demonstrated vascular sensitization by the use of blood vessel spiral rings. I have been trying to determine, however, how I could isolate the minute vessels of a rat to demonstrate sensitization in vitro. In connection with this I have tested the rat's heart muscle suspended in the Dale bath to find out whether it was sensitized to tobacco. Anyone who has worked with strips of heart muscle knows that the cardiac muscle has an idiopathic contraction so that it is very difficult to differentiate on the kymograph between spontaneous contractions and those which we would get from adding tobacco antigen. These are only some of the difficulties with which we are confronted in this work.

I have tried to get around this problem when I stated in my preliminary report* that it was my purpose to show primarily that the tissues of rats which had developed gangrene of the toes by daily intraperitoneal injections of tobacco, were sensitized to tobacco. In demonstrating that the smooth muscle of the intestinal strip was tobacco-sensitive we have indisputable evidence of tissue sensitization. Such sensitization is not only confined to the segment of the gut derived from the injected rat but it involves the animal as a whole and its constituent parts. In making this statement I am simply repeating the fundamental facts of anaphylaxis.

That such sensitization is demonstrable in certain tissues of the experimental animal simply implies that these are shock organs which can be utilized for such purpose. Nobody will deny for example that the liver is the seat of anaphylaxis in the dog. Nobody will deny that the veins of the liver in all probability constitute the shock organ because of the abundance of their smooth musculature. When you wish to demonstrate liver anaphylaxis you work with the dog as your test object. No one will deny that the pulmonary vessels of the rabbit represent its shock organ. If you wish to demonstrate this fact you employ the rabbit as your experimental animal. G. H. Ettinger† showed very

*Proc. Soc. Exper. Biol. & Med., 1937.
†Quart. J. Exper. Physiol., 1931, 1932.

clearly that not only the bronchi but also the pulmonary artery of the sensitized guinea pigs underwent spasm and constriction when perfused with the sensitizing antigen. In these animals the uterine or intestinal reaction always agreed with the arterial. The arterial vasoconstriction invariably followed the bronchial spasm.

In view of these facts, it is conceivable that blood vessel sensitization exists, and that morphologic changes in the toes of our sensitized rats are possibly dependent upon vascular damage due to hypersensitiveness. Whether this is the result of a functional disturbance such as vasospasm of long duration with edema, or superimposed thrombotic arterial occlusion, must still be determined.

In conclusion I wish to say what has impressed me particularly in these experiments is that here we seem to have a bridging of the gap between anaphylaxis and allergy. The gut reaction represents anaphylaxis, as we know it from the classical work of Schultz and Dale. The tissue reaction exemplified by the gangrenous extremities indicates the allergic manifestation of sensitization to tobacco.

Annual Review

RECENT DEVELOPMENTS IN ASTHMA AND HAY FEVER

LITERATURE FOR 1937

SAMUEL M. FEINBERG, M.D.
CHICAGO, ILL.

THE medical literature for the year 1937 indicates that it has been a year of progress in asthma and hay fever. It is the object of this review to parade before the reader the most important developments in this field occurring during the past year and to attempt to coordinate these fragments of contributions into an understandable whole. As in the past, many articles have been omitted from the annual review, because they were either poor, repetitious, or difficult to obtain or to translate. Many others were, no doubt, omitted inadvertently.

England stands unique as the only country in which a concerted national effort is being made in the study of asthma. The Asthma Research Council, now active for several years, is accomplishing a great deal. It is the reviewer's belief that in our country even more could be accomplished by similar united efforts. The Asthma Research Council, in its annual report,[1] lists the activities of the various clinics which it sponsors. Among these the following may be mentioned: At Guy's Hospital preliminary observations have been made which indicate that the approach of an asthmatic attack may be anticipated by a rising sedimentation rate of the erythrocytes. By means of breathing exercises at King's College Hospital, more than 70 per cent of asthma patients are improved or entirely relieved. The effect of various chemical compounds on the isolated lungs of sensitized animals is being studied at King's College.

STUDIES IN CONSTITUTION

Cohen and Friedmar[2] report studies which, if corroborated, may prove of great import in adding to our meagre knowledge of constitutional changes in allergic individuals. They found scorings in the long bones in practically every allergic child under six who had demonstrated food allergy. These scorings are most commonly seen in the lower ends of the tibia and radius and are not permanent. When positive food tests were present without scorings, the authors ignored food factors. In those with scorings, the diet was limited until no new scorings were obtained. Chobot and Merrill,[3] after studying 30 children, came to a different conclusion. In 17 children with definite allergy 13 showed bone scorings. The children with the negative scorings did not differ in

allergic activity from those with positive scorings. In 13 other children, several of whom were feeding problems, 11 showed scoring. They conclude that it is hazardous to diagnose the allergic state on the evidence presented by bone scorings.

An interesting finding made by Debré and his associates[4] is that the bone marrow of all asthmatic young children shows an increase in normal types of eosinophiles which reach a maximum during the attack, sometimes as high as 20 per cent.

The nervous system and the psyche of the asthmatic seem to be receiving increasing attention. On the basis of a study of the constitutional factors in 500 cases of allergic bronchial asthma, Sangiorgi[5] concludes that these patients present a dysequilibrium of the neurovegetative system with special fragility of the respiratory system and "colloidoplasmatic lability."

At Guy's Hospital,[6] 30 unselected adults with asthma were studied with regard to nervous, psychic, or emotional factors. It was found that such factors definitely played a part in 25 of these patients, and that psychic participation takes several forms: (1) Complex determined; (2) development of asthma in an allergic person who temperamentally deviates from the conventional norm of his immediate social group; (3) in an asthmatic individual the attack may act as an arbitrary reflex; (4) the asthma syndrome may be brought on in an allergic subject living under extreme emotional strain, and (5) asthma in an allergic subject may be part of an anxiety state, the height of which may be an asthma attack as an expression of an autonomic reflex outlet. Psychotherapy is suggested by the author as a reinforcement of specific and physical forms of treatment. Depending on the history of the patient, the psychotherapy may be analytical, personality analysis, modification of environmental conditions of the patient, and suggestion.

Clarkson,[7] in an analysis of the nervous factor in juvenile asthma, makes the observation that in almost every case, in varying degree, the following features are common: intensification of emotion; disordered biochemistry; habituation reflex grouped around fear; escape from reality; and an expression of a definite psychosis. Most of the conclusions were reached by an analysis of case histories. In some instances experiments were carried out, two of which may be of sufficient interest to be cited. In the case of a little girl who had fallen asleep with the asthma symptoms unchecked, the author quietly stole up, kept whispering in her ear suggestions to the effect that the asthma would disappear, and in ten minutes the attack ceased. A little girl who gave a positive reaction to egg white was hypnotized the next day, and it was suggested to her that no reaction would occur on testing, which proved to be the case! The next day, without hypnosis, a positive reaction was again obtained.

In a study of 30 children with asthma-prurigo, Rogerson[8] found many in whom special personality features and environmental difficulties were

closely related to the attacks. As an argument that they have a preformed personality feature (constitutional), he cites the finding of a high average intelligence quotient (108+ Binet) which, he argues, cannot be explained on environmental grounds. However, he seems to ignore the fact that the "over-anxiety" on the part of parents and the physical limitations may result in sedentary occupations of an excessive character, which are usually of a mental form. It would be interesting if in his studies he had made comparisons on two series of allergics, one in which there are chronic symptoms resulting in possible environmental influences and another group, such as seasonal hay fever, in which the constitutional factor could be separated. Rogerson does not deny the associated existence and importance of other factors such as allergy and infection.

In a more thorough study Piness and his associates[9] analyzed, by a combination of tests, the intelligence of 145 allergic children from the allergy clinic of the Los Angeles Children's Hospital. These findings were compared with a group of unselected children in the Los Angeles city schools. They conclude that there are no decided differences in the averages and variations of intelligence. The criticism to be offered is that the average intelligence of any public school group cannot be used as a standard for comparison with a clinic group.

There can be no doubt that there is dire need of common sense investigations on the psychic and nervous aspects of asthma, such investigations to be made jointly by allergists and psychiatrists.

PATHOLOGY AND COMPLICATIONS

Pathologic studies continue to confine themselves primarily to autopsy findings of patients dying in asthma or in anaphylactic shock, the status of the heart in asthma and the question of emphysema. Very little experimental work is reported which would tend to throw some light on the basis for the pathology of asthma.

Lamson and Butt[10] analyze the clinical and pathologic findings in 50 published case reports of asthmatics, 48 unpublished cases and 89 without autopsies. They make the observation that under the term of "asthma" have been included cases of tracheal obstruction, pneumoconiosis, and cardiac dyspnea. The pathologic findings in their true asthma cases were similar to those previously reported. Wiseman[11] reports the autopsy findings in a case of status asthmaticus, and Fowler[12] reports autopsies in two elderly individuals dying in asthma. In both reports, the findings were similar to those previously found by other authors. Dahl[13] cites the case of an eleven-year-old boy who had almost immediate anaphylactic death following his twenty-fourth injection of grass pollen extract, the dose being 0.8 c.c. of a 1:10 extract. In addition to emphysema of the lungs and profuse mucous secretion, the autopsy showed a status thymicolymphaticus.

A case of fatal asthma with spontaneous pneumothorax and subcutaneous emphysema is reported.[14] There is very little significance to this report since the evidence in the protocol indicates that death was due to long standing asthma rather than to the pneumothorax or subcutaneous emphysema. Kibler and Watson,[15] in discussing pulmonary emphysema, emphasize the fact that the latter is not only caused often by asthma but also by other conditions. Emphysema caused by other conditions may eventually lead to asthmatic symptoms. Thus the latter situation often presents diagnostic difficulties in deciding whether the asthma is primary or secondary. A dry, warm climate with a moderate altitude is advised in the treatment of emphysema. Small doses of ephedrine frequently administered have been found helpful. Oxygen therapy is sometimes used in severe cases and special abdominal belts to elevate the diaphragm, as advocated by Alexander and Kountz, have been found by them of great help.

Moll[16] calls attention to the fact that the chest deformity in asthma differs from the barrel chest of true hypertrophic emphysema. Based on an x-ray study of 128 consecutive cases of asthma in which 82 showed some chest deformity, he classifies the changes as follows: 1. Early; step-ladder deformity. This is due to the fact that the ribs are in a more horizontal position and the usual smooth even outline of the normal chest due to overlapping of ribs is lost. 2. Late changes; the chest is enlarged in upper part and rounded, the ribs are raised and horizontal, and the upper chest has a ballooned appearance. At about the level of the ninth and tenth ribs, the chest is drawn in and forms a deep sulcus. The lower part of the chest is drawn in and contracted. A "barrel chest" was seen in only 10 per cent of the cases. When the latter occurs, the author believes that it indicates the presence of true emphysema from chronic bronchitis or pneumoconiosis.

A study was made[17] of the heart in 84 cases of asthma, 9 of whom died and 6 of whom were autopsied. Postmortem findings showed little unless there was associated heart pathology, such as valvular disease. Electrocardiographic findings showed a great tendency to myocardial involvement and right ventricular strain. The degree of right strain $[(R_1 + S_3) - (S_1 + R_3)]$ was proportional to the duration of the asthma. This would indicate that the asthma is responsible for that change.

Anthony[18] investigated the circulatory apparatus in 150 patients with asthma. He found a right axis deviation in 43 per cent. Of particular interest in this paper is the discussion concerning the probable harm from the continued use of adrenalin. He cites the autopsy findings of a case of asthma in which marked myocardial changes were found, particularly in the left ventricle. This patient had had long continued administration of adrenalin and caffeine. He also cites the experimental work of Fleischer and Löb in the production of chronic myocarditis in guinea pigs, especially in the left ventricle, by the combined administra-

tion of adrenalin and caffeine. Franz (Virchows Arch. f. path. Anat. 298: 743, 1937) corroborated this finding and showed that other bodies of the methylxanthine chain combined with adrenalin will produce the same effect.

Experimenting on the pathogenesis of asthma, Kallös and Pagel[19] found that the inhalation of finely pulverized antigen caused allergic attacks in sensitized guinea pigs which were identical with human bronchial asthma clinically, roentgenologically, pharmacologically, and immunobiologically. Inhalation of a fine spray of histamine or acetylcholine solution produced attacks in guinea pigs which corresponded clinically to bronchial asthma but the pharmacologic and immunobiologic similarities were not present. Histologic examination of the shocked sensitized animals showed characteristic findings, especially an eosinophile reaction in the walls of the medium-sized bronchi up to eosinophile granulations and other severe changes in the bronchial wall. In the animals receiving histamine or acetylcholine, these changes were not found. The authors conclude, therefore, that these latter substances cannot have any determining significance in the development of this tissue reaction which is typical of bronchial asthma.

OBSERVATIONS OF IMMUNOLOGIC SIGNIFICANCE

The danger in the use of nonspecific protein therapy in allergic individuals is emphasized in the report of Bernstein and Ginsberg[20] who describe the case of an asthmatic woman who became sensitized to milk protein after several injections of the latter.

Anything giving promise of modifying the allergic state is always of the greatest interest to those dealing with allergic diseases. The previous advocation of vitamin C therapy led van Niekerk[21] to experiment further with animals. He studied the influence of vitamin C on anaphylactic sensitization and shock with horse serum in a series of guinea pigs. Avitaminosis C produced no effect on the ability of the pigs to become sensitized nor on their ability to be shocked. Vitamin C added to the diet or to horse serum had no inhibiting effect on the anaphylaxis. Boros[22] describes the case of a ragweed hay fever patient who became jaundiced following the use of cinchophen for a neuritis. With the jaundice there was marked evidence of liver damage and ascites. The hay fever season appeared during his illness without resulting in hay fever symptoms. Subsequently, he recovered from his liver damage but the following ragweed season also failed to cause any hay fever symptoms. Skin tests at that time were positive to ragweed although the conjunctival test was only mildly positive. The liver damage is thought by the author to have produced some change in the mechanism of allergy.

The need for obtaining information as to the degree and speed of absorption and reaction of antigens under various conditions and in various forms led Bernstein and the reviewer[23] to develop an objective

method for this purpose. One forearm is sensitized with several dilutions of reagin. The following day an injection of the antigen is given in a remote site. Reactions occur at the sites previously sensitized. The rapidity of the first reaction, the rate of progression of the reactions to the sites which have higher dilutions of the reagin, and the height to which reactions occur give indications of a quantitative nature. Using this method it was determined that intradermal administration of an antigen results in more rapid absorption than subcutaneous administration. Glycerinated antigens caused no decided slowing of absorption. Adrenalin (0.2 c.c.) added to the antigen caused a delay of about twenty minutes in absorption, after which the rate was only slightly lower than without adrenalin. When the adrenalin was administered simultaneously in the opposite arm practically the same adrenalin effect was noticed, indicating that the major effect of the adrenalin is the generalized constriction of the blood vessels resulting in a temporary prevention of the allergic reaction rather than an effect on the prevention of absorption of the antigen at the site of deposition.

Cowie[24] presents evidence indicating that the skin of an allergic person which fails to react to an intradermal injection of an allergen may be made to react by the passive transfer of his own blood serum into his own skin. The author does not state in what percentage of negative reactors this has been found possible. Neither does he state whether this method would yield results in such conditions as urticaria or migraine, where the skin tests are usually negative. He says that "In some instances, at least, reactions to specific allergens occur as frequently and as vigorously in autopassive transfer areas as in passive transfer areas. Usually, however, passive transfer areas give the larger reactions." Autopassive transfer produces apparently no better results than ordinary passive transfer. These facts are rather difficult to compromise since in our experience and in those of others when negative skin reactions are present passive transfer tests are also negative. Cowie finds further that positive intradermal reactions are often enhanced by autopassive transfer. He concludes that the autopassive transfer method is a practical procedure when passive transfer is indicated, but that it will not replace passive transfer. This piece of work has practical as well as immunologic implications.

Skin reactivity in allergy is receiving considerable attention. Stull and his coworkers[25] have ascertained that the skin sensitizing substance of allergic serum is associated mainly with the pseudoglobulin fraction. A practical contribution has been made by Waldbott and Ascher[26] on the question of skin reactivity in asthma of short duration. In 34 cases of asthma of less than four weeks' duration, the average summation of skin reactions was considerably less than that found in asthma of long duration. Thirty patients gave positive skin reactions on retesting at a later date. The maximum number of skin reactions were obtained

in asthma of about three years' duration. From that time on the tests diminished. On many occasions the reviewer has made similar observations. Patients who failed to show positive reactions early in their career of clinical allergy exhibited positive reactions several months or two or three years later. It is important, therefore, in dealing with cases of early clinical allergy to emphasize the possibility of negative reactions and the advisability of repetition of tests at a later date.

The question of the effect of pollen therapy on skin reactions has been reinvestigated. Harley[27] claims that no appreciable reduction of the prick test following pollen therapy occurs until a dose over 5,000 Noon units has been given. He thinks that the discrepancy in reports as to the effects of pollen therapy on the skin test is due to the failure to realize that a definite dose must be reached before the skin test is affected. Baldwin and Glaser[28] made similar studies. In 98 pollen cases, the skin reactivity was reduced in over half following specific treatment. The mucous membrane reactions were diminished in those who obtained improvement. Skin sensitivity did not necessarily agree with improvement: some who benefited did not show any reduced skin reactivity while in some unimproved cases there was diminished skin reactivity. Quantitative reagin studies in seven benefited cases showed an increase in five and no change in two.

The work of Cooke and his coworkers is confirmed by Harley[27] in the demonstration of a reaction-inhibiting substance in the serum of grass-sensitive patients after treatment with grass pollen. This substance blocks the reactions of normal skin sites to serum-pollen mixtures. The block occurs between the reagin and the allergen. This reaction-inhibiting substance apparently acts by attaching itself to the reagin, thus preventing the allergen from uniting with the reagin. This attachment is not stable, since the skin site is found to be fully reactive to pollen extract twenty-four hours later.

Several blood studies are of interest. The well-known prevalence of asthma among cotton workers induced Haworth and MacDonald[29] to make an attempt to isolate the etiologic factor. They found that the cotton dust contained an appreciable amount of histamine. In 65 card-room workers, the blood histamine was shown to be higher in the average than in normal controls or in cases of chronic bronchitis. The authors make the suggestion that this histamine may be a contributing factor, along with the specific allergens, in the production of asthma in this industry.

The degree of unsaturation of the plasma fatty acids was found in 14 asthma and hay fever cases to be no different from those of normals.[30] In discussing this paper, Chobot mentioned that neither unsaturated fatty acid nor wheat germ oil was of benefit to allergic children in his experience. The question of blood sugar was reinvestigated by Wagner

and Rackemann.[31] In a group of 24 allergic individuals, the fasting blood sugars, even during asthma attacks, were found to be normal. Repeated determinations of glucose tolerance gave quite uniform and normal figures. Even in severe asthma in four patients who used adrenalin frequently the values were normal, providing the adrenalin was not administered immediately before the test. The sugar administration usually caused very little improvement in the asthma. Triplicate determinations were made both on capillary and venous blood.

Changes in blood density have always been suspected as a concomitant of the allergic reaction. Using the method of Barbour and Hamilton, Black and Kemp[32] found a marked increase in blood density in guinea pigs in anaphylaxis, the degree of change being proportional to the intensity of the reaction. A similar concentrating effect in the blood was noted by Black in himself after inducing hay fever by placing pollen in his nose.

In 10 patients with positive reactions to a number of allergens adrenalin (1:1000) 1 c.c. was given subcutaneously,[71] and then at intervals cutaneous and intracutaneous tests were made. The adrenalin reduced the reaction appreciably and at times markedly. Weakly positive reactions were apt to become doubtful or negative. The maximum effect of the adrenalin occurred within fifteen to thirty minutes. No effect was present after one hour. There was no correlation between the effects of adrenalin on the skin reactions and those on the blood pressure and the pulse.

The above contributions in the immunology of asthma and hay fever and many more of even greater importance which are not reviewed here because they belong more strictly to the annual review in immunology indicate the steady progress in this phase of allergy. Since it is the reviewer's belief that the future of allergy depends mainly on developments in immunology this augurs well for progress in that phase of medicine.

ATOPENS AND ATOPY

New specific causes of asthma and hay fever continue to appear and additional instances of less common types of allergy are reported. A grain elevator worker who had rhinitis and asthma was found to be sensitive to corn cockle seed found in wheat.[33] Corn cockle *(Agrostemma githago)* belongs to the *Silenaceae* family, grows in grain fields and its seeds are frequently found in wheat and flours, particularly of the darker types. The patient cited had strongly positive skin tests and reagins to corn cockle seed, and improvement was obtained by desensitization. In 30 other patients tested with this antigen, 5 obtained positive reactions. The author points out the possible importance of this antigen as an ingestant. Weston[34] describes two patients who had symptoms of asthma from derris root used in a flea powder. Derris is a genus of

tropical shrubs comprising about 40 species and being increasingly used for insecticidal purposes. The patients were not sensitive to pyrethrum.

Chiorazzo[35] reports three cases of allergic asthma who were sensitive to the silk shreds used in the stuffing of pillows and quilts. He thinks the probable cause of the symptoms was the sericin contained in the silk. An instance of hypersensitiveness to a powder commonly burned for the relief of asthma is recorded by Swineford.[36] This powder contains Stramonium leaves, swamp cabbage, *Lobelia inflata* and potassium nitrate. By skin and passive transfer test the patient was found to be sensitive to all three of the organic ingredients. Swineford ventures the opinion that some people have their asthma prolonged by specific sensitiveness to asthma powders or cigarets.

Of all drug allergy, that due to aspirin is probably the most common. Prickman and Buchstein[37] analyze a series of 62 cases of aspirin sensitiveness. The most common type of allergy was respiratory. Asthma is the most serious form, all fatal cases having been of this type. Gastrointestinal symptoms and angioneurotic edema were also fairly frequent. Skin tests are nearly always negative. The most severe symptoms are encountered in patients with nasal polyps.

Criep[38] reports two interesting cases of allergy due to dyes. One was a dermatitis following the painting of Easter eggs. This was proved to be due to the oil red N-1700 and to oil orange 7078. The other case was an asthma following the use of tinted metaphen. This was traced to the orange I, which gave negative patch test or scratch test but resulted in systemic reactions.

Fungi.—The rôle of fungi in respiratory allergy is receiving increasing recognition. A case of respiratory allergy due to inhalation of grain smuts about grain elevators is described by Wittich and Stakman.[39] The attacks were not seasonal but would occur at any time of the year that his duties would take the patient around flour dust. Tests showed reactions to a number of smuts as well as to *Alternaria,* yeast, and ragweed.

Bernton and Thom[40] found four cases giving a positive skin test to *Cladosporium.* In three of these they obtained good results by desensitization. There are not enough data in the case reports cited to indicate the nature of the allergy. In the reviewer's experience, allergy to *Cladosporium* fungi is very common, occurring in a great portion of individuals who are sensitive to *Alternaria.* The large numbers of *Cladosporium (Hormodendrum)* spores in the air during summer and fall in the middle west would be sufficient in itself to make one suspicious that this may be an important allergen.

A study of the coastal areas of Texas with respect to fungi as causes of asthma and hay fever was made by Prince and Morrow.[41] They exposed plates, for two minutes each, daily from September of one year through June of the next. They compared this with exposures indoors

in the home of a patient sensitive to molds. Contrary to the reviewer's experience in the Chicago area in which it was found that the outdoor air contained many more spores than the indoor air unless the latter had an unusual environment, Prince and Morrow found that the indoor figures were equal or higher than those of outdoors. Their plates showed a high count of fungi. They isolated a large number of species, including a large number of *Aspergilli,* a number of *Moniliae* and a few strains of *Penicillium. Alternaria* was never found by them. *Helminthosporium, spondylocladium,* and *cephalosporium* were found rarely. The mold season is in the winter months. In 46 cases of respiratory allergy selected from about 200 respiratory cases, skin tests with molds (1:500 intradermally) gave reactions in 37. Of the reactions obtained the following were the most frequent: *Monilia sitophilia* 17, *Monilia geophila* 13, *Aspergillus niger* group 22, *Penicillium* 15, *Helminthosporium* 5, *Alternaria* 4, *Trichoderma* 3, *Aspergillus sydowi* 2, *Aspergillus japonicus* 2, *Hormodendrum* 2, *Cladosporium* 1, and unclassified 7. Of this group, 21 were treated with molds and 20 obtained improvement.

An analysis of 90 cases of mold allergy was made by the reviewer.[42] Seasonal aggravation is the rule in the Chicago area. Seventy patients of the series began their symptoms before the age of ten. Combined nasal and asthmatic symptoms were present in 55, asthma alone in 9, and nasal symptoms only in 26. Allergy due to molds only was present in 25, while in 58 there was associated pollen allergy. Of 60 who had specific treatment, 48 obtained excellent results, 9 fair, and three were unimproved.

The origin of the allergenic factor in old cotton, feathers, or kapok is still a puzzling problem. Wagner and Rackemann[43] subjected new kapok to a number of procedures and tested the extracts of the treated materials on patients who did not react to the new materials. They found that kapok fiber which had been sterilized failed to develop a skin test substance after six months of aging, even though it was exposed to light, dark, or cold. Exposures to carbon dioxide or oxygen had no effect. On the other hand, the implantation of molds in the kapok or cotton caused the development of the active principle, especially if the molds were taken from samples of old kapok, old cotton linters, or house dust. The mold extracts alone did not give reactions in most of these individuals. They conclude that the active principle in old kapok depends on the interaction of the kapok and the molds growing in it. Since Cohen and his coworkers had previously come to an entirely different conclusion as regards old cotton (house dust), this question must await further developments.

Pollen and Pollinosis.—In a series of 108 pollen cases in Philadelphia and vicinity, Tuft and Blumstein[44] found only one who was a pure tree pollen case and 7 who had tree pollinosis in addition to others. Related tree pollens showed varying degrees of skin and passive transfer reactions

and from this the authors conclude that it is important to use in treatment the species most common to the environment of the patient. The same authors[45] made a similar study of plantain hay fever in the Philadelphia area. Plantain allergy was found in 7.7 per cent of 180 hay fever cases. Skin tests were positive in a much larger percentage. Passive transfer studies showed that the reagins of English and common plantain are mutually exhausted, and the authors infer that they contain a common antigenic factor. There is no such relationship between plantain and timothy. The authors conclude that plantain-sensitive patients must be treated with plantain pollen.

Two new causes of hay fever are reported. McMinn and Graham[46] tested 58 patients in California with pollen of *Caprosma baueri endl.* (mirror plant) and obtained positive reactions in 13. The plant is an ornamental shrub used in great numbers in gardens, parks, and along the streets throughout the state. It pollinates from April to late June. Langley[47] reports a case of hay fever in a nurseryman due to the pollen of Piqueria *trinervia.* This is a plant belonging to the *asteraceae* of the *Compositae.* It is native to Mexico and Central America and is cultivated in nurseries in this country, pollinating in November, December, and January. The patient was sensitive to this pollen and had hay fever from it during the months mentioned. He did not develop sensitivity to piqueria until he became a ragweed pollen sufferer. Of 52 allergic patients tested with piqueria, 4 reacted. All of the latter were sensitive to ragweed. Not all ragweed cases, however, react to piqueria.

With alum-ragweed precipitate, Zoss and his coworkers[48] sensitized guinea pigs which were later shocked by intravenous injections of pollen extracts. Local and systemic reactions in ragweed sensitive patients from intracutaneous and subcutaneous injections of comparable protein nitrogen concentrations were similar. Following subcutaneous injections of passively sensitized individuals they demonstrated "a slight delay in the absorption of the active pollen fractions." Comparing a series of extract-treated patients with 24 patients treated with alum-precipitate, the results of the latter were not as good as the former. However, the treatment appears to have been identical with that used with ordinary extracts with regard to time intervals, progression of doses and maximum doses reached.

Polysaccharides from several varieties of pollen were isolated by Service.[49] These preparations did not give skin reactions in allergic human beings or animals but were capable of preventing anaphylaxis when injected in guinea pigs prior to the shocking dose of homologous protein. Service believes that from the experience he has had with two patients, the polysaccharide is capable of lessening pollen asthma. His data and results are not convincing, since both patients received

regular desensitization therapy prior to polysaccharide administration and in both instances sufficient asthma was present during the season to require adrenalin injections.

Gelfand and his associates[50] claim that the sedimentation and precipitation, and possibly deterioration, of pollen and other allergenic extracts which follows vacuum filtration are due to the removal of the CO_2 during the suction process. They, therefore, recommend the use of positive pressure of 10 to 20 lbs. with CO_2 or air for filtration.

Just about when the standard for pollen counting is becoming universally established, a disturbing bombshell of doubt is thrown into our camp. Cocke[51] claims that Scheppegrell's table for velocities of fall in feet per second was incorrectly calculated and as a result the reports of pollen concentration per cubic yard based on his formula are much too low. Scheppegrell's error lies in the fact that in Stoke's formula $V = \frac{2\ g\ r^2}{9\ K}$ he used the diameter squared instead of the radius. As a result of this error, for example, a pollen with a diameter of 20 microns should have a formula of 7.3 N instead of 1.8 N (where N = no. on 1 sq. cm.). Cocke says that for scientific accuracy the actual size of each pollen grain should be considered in calculating the pollen concentration of the atmosphere. Allowance should also be made for the lower velocity of fall of rough and spiculated pollen. The author recommends that the number of pollen per cubic yard be computed by the gravity method from the formulas given in his table. To the reviewer's mind it seems rather impractical to attempt to compute every type of pollen (and mold spores, etc.) on the slide in terms of cubic yard. It is much more practical to utilize a unit area on the slide as a standard. Even though the number of smaller particles is thus underestimated, the fact is that the total mass of allergen is the more important consideration in the production of allergic symptoms. Since the number of small particles suspended in a unit of air will fall in smaller numbers on a unit area than the large particles, the recording of a smaller number gives a better conception of the lesser effect from the allergic standpoint.

The question of antigenicity of various portions of the plant has been studied again by Farmer.[52] By cutaneous tests on grass-sensitive patients with pollen and seed extracts of a number of grasses, he obtained no reactions from the seed and thus concludes that there is no immunologic relationship between the pollen and the seed of grass.

An attempt was made by Berkoff[53] to evaluate the effect of various nonpollen allergies on the seasonal hay fever symptoms of 149 employees of a large department store in New York City. He concludes that the rôle of nonpollen inhalants in the symptomatology of hay fever, with the possible exception of dust, is negligible. He has not noticed any effect of foods on the course of hay fever. The value of this report is

subject to doubt when we realize that the data were gathered by the questionnaire method and that there is no indication that any tests were made.

Atopic State.—In a series of 2,829 allergic patients, Rynes[54] found 644 reactions (intradermally) to the dander of cat, horse, dog, and rabbit. Of these 367 patients only 24 per cent were aware of their dander sensitivity. Elimination of exposure was sufficient to obtain good results of 87 per cent. In a few, hyposensitization was necessary. More than half of the dander-sensitive patients were under twenty years of age. In the reviewer's experience, a frequent unsuspected source of exposure to horse dander is the dust and the hair from the horse fertilizer used in cities on lawns, parks, and boulevards.

The antigenic relationship of old kapok, house dust, and old chicken feathers was studied by Wagner and Rackemann.[55] They conclude that these antigens are not identical. They made no attempt at any quantitative study, i.e., using the antigens in dilutions in which all would give equal reactions.

There are surprisingly little data attempting to analyze the incidence and types of allergy of communities or districts. In a community of 700 (Jackson, Louisiana), comprising secondary school children and college students, an inquiry was made[56] as to the occurrence of allergic symptoms. Of these, 95 had major allergy while in 217 of the remainder minor allergic symptoms were present. The most important minor allergic manifestations in their order of frequency were: indigestion, urticaria, eczema, and migraine. As causes of minor allergy the foods at the top of the list were: cabbage, onion, melon, strawberry, tomato, banana, chocolate, pork, peach, beef, peanut, cucumber, radish, crab, and oyster.

In a study of 43 patients with respiratory allergy who had clinically proved vegetable food sensitiveness, Withers[57] found that there is not as close an agreement between foods as antigens as there is in their botanical relationships. A patient who is clinically sensitive to one food in a botanical family has about a 50 per cent chance of being sensitive to others in the same family. If he is sensitive to the least common etiologic factor of the family he is more likely to be sensitive to other members of the group. This in itself, contrary to the impression created by the author, would tend to imply a common antigen in the group. It is interesting to note that practically no clinical relationship was found to exist between potato and tomato of the *Solanaceae* family. Tomato, wheat, peanut, watermelon, peach, apple, orange, onion, and English walnut were the most common etiologic factors in their respective families.

Rinkel[58] reemphasizes the importance of complicating allergens in the consideration of treatment of pollinosis. He regards foods as par-

ticularly important and stresses the use of the leucopenic index to diagnose the food allergy. He finds no confirmation of the usual claim that food allergy is less common in adults.

Insufficient air moisture in the home during the winter months is responsible for the causation of prolonged asthmatic attacks, according to Parlato.[59] He finds that with a normal relative humidity (between 40 and 55 per cent) asthmatic patients respond more readily to the usual therapeutic procedures. He warns against the use of belladonna, stramonium, and similar drugs because they result in a diminution of the mucous secretions. The experience of the reviewer has been identical with that of Parlato.

REGIONAL OBSERVATIONS ON PLANTS AND POLLEN

North America.—In Alabama, Weil[60] divides the hay fever plants into three groups: the trees, grasses, and weeds. The tree season is from February to the middle of June and is caused by elm, oak, hickory, black walnut, and pecan, the latter being the most important. The grass season, beginning in March and ending in October, is caused by the following, in order of sequence of pollination: blue grass, rye grass, Bermuda grass, Johnson grass, fescues, Paspalums, panic grasses, foxtail, sweet grass, gama grass, brome grass, and plume grass. The fall season is caused by giant and short ragweed, cocklebur, and marsh elder and begins about the first of September. In a total of 70 seasonal hay fever cases, 22 were of the summer variety and of the latter only 7 reacted by skin test to grass pollen. The remainder did not react to pollen cutaneously, intracutaneously, conjunctivally, or nasally. They also failed to react to a number of mold antigens.

A clinical and atmospheric study of Seattle was made by Schonwald.[61] The tree season there is from February until July and among the trees of importance are hazel, alder, birch, poplar, balm of Gilead, cedar pine, oak, maple, mountain ash, cedar, tamarack, and red fir. The grass season is from April until August and is due to June grass, orchard grass, rye, and velvet grass. The plantain season is an important one and extends from May until frost. Lamb's quarters, curly dock, sheep sorrel, and pigweed also contribute to hay fever production. In addition to the pollen, he has found the brake fern to be a cause of respiratory allergy. Mold spores are frequently a contributing cause and in many instances even the sole cause of allergic symptoms. The most common fungi found by Schonwald in the Seattle area are *Rhizopus, Aspergillus, Penicillium, Hormodendrum,* and *Trichoderma.*

Based on yearly ragweed studies of almost 100 localities, Durham[62] tries to evaluate their comparative freedom from pollen and their desirability as hay fever resorts. He computes a ragweed pollen index for each locality by allowing 1 point for every day with a pollen count over 25, 1 point for each 100 of the maximum pollen count, and 1 point for

each 200 of the season's total. Thus, localities having an index under 1, which would be favorable for hay fever cases, are Phoenix, Los Angeles, Sacramento, Jacksonville, Miami, Reno, Portland (Oregon), Amarillo, El Paso, Seattle, Spokane, Father Point (Que.), Prince Albert (Sask.), and Mexico City. Some of the "resorts" have the following indexes: Bar Harbor (Maine) 8; Eastport (Maine) 6; Upper Dam (Rangeley Lakes) 2; Alpena (Mich.) 21; Isle Royal (Mich.) 2; Marquette (Mich.) 21; Petoskey, 13; St. Ignace 13; Sault Ste. Marie 6; Duluth 44; Tower (Minn.) 6; Lake Placid (N. Y.) 7; Saranac Lake 5; Eagle River (Wis.) 13; Cochrane (Ont.) 2; Parry Sound (Ont.) 8; and Port Arthur (Ont.) 7.

Alberta is divided by Jamieson[63] into three zones. The northern zone has only spring hay fever, due mainly to poplars. The central zone has spring and summer hay fever, the latter due mainly to June grass and timothy. The southern section also has fall hay fever caused principally by Russian thistle and sage. In the southernmost section of Alberta a small amount of ragweed is found.

South America.—Several reports dealing with hay fever conditions in South America have appeared. Gonzalez and Lombardo[64] discuss the principles of pollinosis as applied to hay fever plants of Paraguay. They include also a list of the wind-pollinated plants of Uruguay, but they do not give any clinical, field, or atmospheric data.

An excellent article by Bozzola[65] deals with a botanical survey of Argentina in which the country is divided into nine zones distinguished by varied topography, elevation, and climate. Lorenzo R. Parodi, professor of botany in the Buenos Aires and La Plata Universities, assisted in obtaining the botanical data. Accompanying the article is a map with a list of some 75 wind-pollinated plants of Argentina. The article notes the geographic distribution, dates of pollination, and probable clinical importance of most of the plants. The author states that ragweed *(Ambrosia tenuifolia)* is common in Zone 1, which consists of the populous province of Buenos Aires. He also mentions *Ambrosia artemesiafolia* and *elatior* together with *Artemisia peruviana* and *Ambrosia scabra* as being found in other zones. English plantain is mentioned as of second importance throughout the country. Russian thistle *(Salsola kali)* and Mexican firebush *(Kochia scoparia)* are of considerable importance in southern and western parts of the Buenos Aires province. The grass season in higher altitudes begins in September and continues to December. Species flourishing in other areas, for example, *Lolium multiflorum,* are said to pollinate from November until February. The ragweed and Russian thistle season extends through January, February, and March. Bozzola estimates that 2 per cent of the population of Argentina are affected by pollinosis.

A local survey of the hay fever situation in the vicinity of Bahia Blanca is reported by Bouzat.[66] He estimates that 4 to 6 per cent

of the population in the city have hay fever. In 80 per cent of the patients, positive reactions are obtained with Russian thistle and Mexican firebush. The hay fever season starts in December and continues through February. During most days of January and February he finds 80 to 150 pollen per square centimeter on glycerin covered slides, and sometimes as high as 225. He says that a large part of the pollen found on the slides is made up of pollen from Russian thistle and Mexican firebush.

Australia.—Sharwood,[67] in a continuation of his pollen study of Melbourne, notes that the grass season is the most important there. It begins the latter part of September and reaches a peak about the middle of November and is practically terminated by January, although a small amount of the pollen prevails until March. The plantain, beginning at about the same time as the grasses, has its maximum flowering period in December and continues with fair amounts until March. Sorrel, dock, and Chenopodium were of some importance. The trees pollinate from August to October and although the pollen production is considerable the author does not know of any tree pollinosis.

Durham[68] emphasizes the importance and limitations of mold spore studies by the slide method. He gives the results of *Alternaria* counts from March to November, 1936 in 10 representative localities and counts from many other localities for the summers of 1933, 1934, and 1935. The greatest *Alternaria* region seems to be the central states (from the Rockies to the Appalachians), both coasts, and the deep south being comparatively free. He emphasizes the fact that this finding may be the cause for the discrepancy in the views on the clinical importance of mold allergy as expressed by allergists in diverse parts of the country.

DIAGNOSTIC PROBLEMS

Now and then there crops up a report tending to discredit the value of skin tests. One of the favorite methods is the reporting of positive tests in control subjects in almost as high a percentage as in allergics. Thus, Pearson[69] describes a series of intradermal tests with horse dander, chicken feathers, wheat, egg white, and horse serum albumin on three groups of individuals: allergics, nonallergic individuals with a family history of allergy, and those without any such family history. The percentage of reactions in these three groups to horse dander, for example, were respectively 75, 50, and 37. It is difficult to explain these and similar findings. It is absolutely contrary to our experience. The high incidence of reactions would speak most likely for a fault in the materials.

As has previously been mentioned,[26] it has been demonstrated that in asthma of short duration the skin tests are apt to be negative. It behooves one, therefore, to advise repetition of the tests at a later date if the incidence of positive diagnosis is to be maintained at a high level. The

method of autopassive transfer described by Cowie[24] may be of aid in the diagnosis in some instances. The importance of the diagnosis of complicating sensitizations in pollinosis is stressed by Clarke.[70]

The question frequently arises to what extent adrenalin administration affects the reliability of skin testing. Swineford and Grove[71] planned their experiments to solve the problem. They found that 1 c.c. of 1:1000 adrenalin has a definite effect in diminishing the skin test, but that no effect is discernible after one hour. Blumstein[72] describes the nasal pollen test as the most valuable guide in the diagnosis of clinical pollen allergy. The ophthalmic test gave reactions in some patients who were not clinically sensitive.

Squier and Madison[73] make a contribution to the problem of diagnosis of food allergy. In a series of 84 allergic patients a total of 200 food tests with hematologic responses showed that an increase of 50 or more eosinophiles per cu. mm. was present in practically all cases in which there was a leucopenic response, and that it was also present in some cases in which the leucopenic response was absent. With mixed meals containing allergenic foods, even though the leucopenic response may be absent, the eosinophile response may be seen. They conclude that simultaneous counting of both eosinophiles and leucocytes materially increases the diagnostic accuracy of the leucopenic index. Earlier in the review, mention is made of the use Cohen and Friedmar[2] made of bone scorings in the diagnosis of food allergy.

A method of measuring the progress in asthmatics is described by Otto.[74] An instrument was constructed which measured in term of degrees the force of the expiration. He found that the figure for normal healthy men was 91° to 135°, in healthy women 69° to 109°. In 50 per cent of a series of asthmatics the reading was under 18° and in the majority of the others it was not over 65°. The author employed the determinations as an indication of the progress of the patient and the value of the management. Thus, he mentions the resultant increase in the expiration pressure when patients were placed in a low pressure chamber (equivalent to an altitude of 5,000 meters). The effects of medication of various types could also be objectively determined. Breathing exercises raised the pressures on an average from 15 to 35°. They found similar diminution of the expiration pressure in emphysema, but the results were less marked in other respiratory diseases.

A contribution to which attention has already been called[16] is the observation of early emphysematous changes in the chest, physically and roentgenologically, in the form of the "stepladder" appearance of the ribs.

One of the most interesting contributions of the year in the field of asthma is the study made by Swineford and Magruder.[75] It is well known that only a small portion of cases of heart failure of the types

known to cause cardiac asthma actually result in asthmatic symptoms. The question naturally arises, what is the additional contributing factor which determines the onset of asthma? The reviewer had observed for many years and taught to his students that patients with cardiac asthma frequently give a history of having had allergic asthma or asthmatic bronchitis in previous years. It has also been the reviewer's experience to have under his observation cases of bronchial asthma without any cardiac findings return with asthmatic symptoms and heart failure after several years of absence of asthma. These observations have led to the impression that in addition to the special type of heart disease and cardiac failure an asthmatic or allergic habitus was the final factor responsible for the inciting of the cardiac asthma. Swineford and Magruder studied 47 cases of heart disease with wheezing from the standpoint of cardiovascular findings, origin of the asthmatic symptoms in relation to the heart disease, the presence of clinical allergy, and the family history of allergy. Of this group, 28 had sufficient asthma to be considered as troublesome. In 21 of the latter the asthma preceded, in mild form, the nocturnal paroxysmal orthopnea by many years. Over 85 per cent of the cardiac asthmatics gave a history of other allergic manifestations, such as hay fever, migraine, or urticaria. Of 23 who were tested with a series of 20 allergens intradermally, 21 gave positive reactions. In 66 per cent there was a positive family history of allergy. In almost one half of the group the wheezing had been present for many years. In 19 cases of congestive and anginal failure with slight asthma, the allergic family history and skin test findings were about the same. In a study of 14 control cases of congestive and anginal failure without asthma, allergy was present in 7, family history of allergy in 2, and skin tests were positive in 7 out of 9. The authors conclude that their evidence indicates that the presence of wheezing in paroxysmal nocturnal dyspnea is in the majority of cases a sign that the patient has previously had asthma of some degree or that he is an allergic individual in whom the onset of the asthma is provoked by the loss of cardiac reserve, and that the changes incident to the attack of dyspnea are the so-called "nonspecific exciting factors" which initiate the wheezing.

The facts which make the above study less convincing are: the unusually high incidence of allergy and positive skin tests in the cardiac asthmatics and the high incidence of allergy and positive skin tests in the control group.

OBSERVATIONS ON TREATMENT

The periodic literature teems with papers dealing with the treatment of allergic conditions. It is in this phase of allergy that the tendency for repetition, exaggeration, and generalization reaches a maximum. It is not surprising, therefore, that the majority of these articles are useless for the purpose of review and have been deleted

from this summary. While it is admitted that not all the worth-while papers on therapy are included in this review, nevertheless, those that are reviewed are quite representative.

Hay Fever.—The question of the choice of perennial or preseasonal method of hay fever treatment has been again revived. Spain and Fuchs[76] made a survey of 950 adults with hay fever, of whom 692 were treated preseasonally and 258 perennially, from 1932 to 1937, inclusive. The percentage of good results was greater in later years and the fluctuation with pollen counts was less, due probably to increased dosages. Of the perennial cases, after one season of preseasonal treatment, 94.2 per cent had effective relief. Of the preseasonal cases, 73.4 per cent had effective relief. The incidence of constitutional reactions was 0.26 per cent in preseasonal and 0.15 per cent in perennial cases. The preseasonal cases began their treatment about three months before the season. About 17 injections were given weekly, and at four to seven day intervals during the season. The perennial cases received monthly injections, while during the season the injections were given "at more frequent intervals, in some cases as often as once a week."

The comparative results obtained by these authors are striking and should evoke a great deal of thought and experimentation. The outstanding criticism of this survey is that the comparison of the two groups as classified by the authors may not be a fair one. In one group are the perennial cases *all* of whom have had a previous course of preseasonal treatment. In the other group are included all the preseasonal cases, whether they had several seasons of treatment or only one. Since many patients only take one season of treatment and since the poorest results are usually obtained during the first season, it would seem that the preseasonal group selected on the above basis would, a priori, be expected to manifest a poorer average than perennial patients (who had two or more years of treatment). One wonders whether the difference between the preseasonal and perennial groups would be as decided if in the former group were included only those who have had at least two seasons of treatment. This criticism is in a sense a self-criticism because the reviewer sides with Spain and Fuchs in believing that better average results are obtainable with the perennial method.

Rapid hyposensitization, particularly as regards pollen therapy, is again discussed by Waldbott and Ascher.[77] They use that method especially when the time before pollination is short or during the pollen season. In order to be safe, the initial dose must be low and marked local edema should be avoided. Adrenalin is contraindicated because it tends to mask the local reactions. The authors report that they frequently reach a dose of 7,000 or 8,000 pollen units in five or six days. In considering rapid hyposensitization, one should keep in

mind that two questions are involved. One question is: How safe is it? At what short intervals can one give doses of an antigen without having a cumulative effect, i.e., a preponderance of retention over elimination of the antigen? The second problem is: How rapidly can the tissues acquire a tolerance so that the rapid *increases* of the antigen doses may be not only safe but effective? On the first question our observations on absorption and elimination of antigens[23] would indicate that doses twice daily are probably safe and injections more frequently may be unsafe. However these considerations deal only with standard and equal doses. They do not take cognizance of the fact that with increasing doses the tolerance may lag far behind the rate of increase of the antigen. On the latter point very little experimental information is available.

Waldbott and Ascher[78] analyzed a series of 397 cases of fall hay fever treated during the 1936 season. In general, those who received low final doses had less relief than those attaining higher doses. A maximum dose of 30,000 pollen units of combined ragweed pollen usually gave the best results; doses higher than that gave no better results. With relatively low final doses treatment was more effective in the more sensitive cases than in the less sensitive ones. The latter required larger doses in order to obtain the same degree of relief. The authors believe that it is likely that the actual amount of pollen injected is of less significance for the relief of symptoms than the degree of local response. The observations and principles expressed in this paper are in complete conformity with the experience of the reviewer.

The need for a detailed analysis of many factors concerned in the treatment of hay fever is filled by the paper of Clarke and Leopold.[79] They analyzed a series of 612 hay fever cases, treated for one or more seasons during the years 1921 to 1936, inclusive, and who have had at least 8 injections in one season, begun prior to July fifteenth. Analyzing their figures they conclude that prophylactic ragweed treatment is more likely to give good results: (1) in males; (2) in younger persons, particularly below twenty years of age; (3) in private practice; (4) in those with weaker skin reactions; (5) in those who have had constitutional reactions; (6) in those without asthma; (7) with low maximum doses, less than 800 Cooke units (0.015 mg. total N.); (8) when pollen injections are omitted during the season, although a few do better with coseasonal doses; (9) when other allergens are discovered and appropriately treated. Treatment is affected very little by strength of eye reactions, atmospheric pollen concentration, or successive years of treatment. Perennial treatment was less effective than preseasonal, although a few persons do better on the former method. This constitutes a remarkable piece of clinical analysis, but

it is also one containing a sufficient number of conclusions at variance with clinical impressions of many allergists to serve as a stimulus and a challenge for further work.

The frequency and causes of constitutional reactions are analyzed by Furstenberg and Gay.[80] In 43,771 allergen treatments, there were 87 constitutional reactions. Among the pollen cases in private practice, 11.7 per cent of the patients and 0.16 per cent of the injections resulted in reactions. Of the clinic cases, 5.9 per cent of the patients and 0.33 per cent of the injections reacted. The authors claim that they have never experienced an intravascular or back-seepage reaction. As the most important causes of constitutional reactions, they list the individual tolerance of the patient for a given dose and the change from a large volume of a weaker extract to a small volume of a stronger extract. As lesser causes, they list the use of too concentrated extracts, too frequent injections, too large an increase in dose, errors in dosages, too large an initial dose, and improper technique of administration. Furstenberg and Gay admit that for reactions in one-half of the clinic cases and two-thirds of the private cases they have not been able to demonstrate any evident cause.

A great deal of interest has been centered in the past year on the question of oral pollen therapy. While the recorded observations are only few in number, many workers are in the process of evaluating this method.

The most extensive report is that of Stier and Hollister.[81] They claim to have obtained satisfactory results in 78 per cent by oral pollen therapy in the northwest area. The best results were obtained by coseasonal treatment. The doses were 3 to 4 drops of 1:10,000 extract to a maximum dose of 21 drops of 1:100. Most patients required a quantity of the 1:100 solution daily. At times mild systemic reactions occurred but no severe reactions were noted. The pollens used consisted of a large variety but apparently did not include ragweed. McGrew[82] began to use pollen orally because it was pointed out to him that hay fever sufferers were obtaining relief by eating honey (presumably containing pollen), produced in their vicinity. He used a 1 per cent pollen extract, giving it coseasonally, 1 to 3 drops, three times daily, or for the immediate relief of an individual attack. Overdosage caused aggravation of symptoms. Of 33 patients treated in this manner 29 improved. Those with multiple allergy or with asthma did not do well.

Urbach[83] administers at the beginning of the hay fever season tablets made from the papain-treated and pepsin-treated grass seeds and flowers, one hour before each meal. In addition, the patient takes one to two teaspoonsful of the following mixture in a half glass of water: dilute hydrochloric acid 25, dry pepsin 25, water to 200 parts. By this method the following results were obtained in 102 hay fever cases in

1936: 74 per cent were practically symptom-free, 22 per cent had definite improvement, and 4 per cent were unaffected. In the asthma cases the results were approximately the same.

In a paper to be published, T. B. Bernstein and the reviewer[83a] showed that in a series of ragweed cases practically no beneficial results were obtained by oral ragweed pollen therapy in spite of the fact that sufficient material was administered to produce marked gastrointestinal symptoms in several of the patients. Previous to the clinical trials experiments on gastrointestinal absorption of ragweed antigen, as demonstrated by passively sensitized areas, demonstrated that there was circulating antigen less than 1/5,000th part of that present after subcutaneous injection. C. Bernstein, Jr., and Kirsner[84] also failed to obtain reactions in passively sensitized sites after giving 5 grains of ragweed pollen orally.

The Asthmatic Attack.—In 16 cases of severe asthma in which the usual palliative treatment had become unsuccessful, Herrmann and Aynesworth[85] gave theophylline ethylenediamine intravenously in doses of 0.24 to 0.48 gm. diluted to 10 c.c. with normal saline. Of the 41 injections given, 31 gave prompt and persistent relief. While reactions to the drug were common, consisting mainly of warmth, nausea, and vomiting, rarely were the symptoms marked.

In 11 cases of asthma Greene, Paul, and Feller[86] also obtained good results with theophylline ethylenediamine. They attribute the beneficial results to the fall in venous and intrathecal pressures.

Propadrin hydrochloride, an analogue of ephedrine, gives relief in asthma, hay fever, and urticaria, according to Black.[87] Doses of 24 to 48 mg. were used, and the drug were preferable in many instances because it did not produce symptoms of nervousness or insomnia. The reviewer's experience indicates that propadrin fails to relieve too many patients to be the drug of choice, that it will sometimes produce nervous reactions similar to those produced by ephedrine, and that its real usefulness lies in its use as a substitute for ephedrine when the latter has lost its effect or when it cannot be tolerated.

From an experience with 16 cases of status asthmaticus, Kahn[88] advises first the use of epinephrine intravenously; this relieved 6 out of 11 in which it was tried. When this measure fails he tries ether and olive oil rectally. He finds that 5 to 7 ounces of the mixture (equal parts) administered over a twenty-minute period will produce results in about half of the cases. For several years the reviewer has used ether rectally in status asthmaticus and can corroborate its usefulness. However, in our experience we have found it rarely necessary to exceed two ounces of the ether at the first dose, which can be repeated two or three times at intervals of several hours, provided the patient is not asleep. In another paper, Kahn[89] describes several cases

of intractable asthma or status asthmaticus relieved of symptoms for weeks or months following the induction of surgical anesthesia by ether inhalation for about twenty to twenty-five minutes.

Tribromethane (avertin) rectally, in doses of 60 mg. (50 to 70) of the fluid per kg. of body weight, is described by Fuchs[90] to have given results in 25 cases of status asthmaticus. The five case histories cited do not mention, however, the previous use of ether, which may be just as, or perhaps more, effective. One should be mindful of the fact that ether is a safer drug than avertin.

Special Methods.—Improvement in an asthmatic patient following the use of adrenal cortex by mouth is reported by Carl.[91] Since the paper was written only several months after treatment was begun and since only one case is reported, the significance of such a report is doubtful.

In the last three or four years, there have been a number of papers lauding the benefits of intratracheal instillation of iodized oil in asthma. Criep and Hampsey[92] undertook the job of evaluating this form of treatment. Of 30 asthmatic patients treated by them with iodized oil, 4 obtained prolonged relief and not all of the latter were chronic cases. In some cases in which allergy was demonstrated, there was no loss of clinical sensitivity to substances to which they were allergic. A questionnaire sent by the authors to 335 allergists and bronchoscopists brought 230 replies, of which 64 gave the results of iodized oil treatment in 267 cases of asthma and 938 of asthmatic bronchitis. In the asthma cases the results were: cures 1.9 per cent, improved 24.7 per cent, and failures 73.4 per cent. In the asthmatic bronchitis cases there were 0.8 per cent cures, 22.8 per cent improved, and 76.4 per cent failures. Many untoward reactions were reported. The authors note that fatalities also occur.

Another form of therapy whose efficacy is open to doubt is urinary proteose. Libman and Bigland[93] obtained benefit from treatment with urinary proteose in some patients with asthma, but the extent of the results did not exceed those obtained from injections with ordinary peptone solutions. The authors say further that the zone of erythema occurring at the site of an intradermal injection of urinary proteose is not a specific reaction but is probably only a local toxic effect.

Intranasal zinc ionization is again receiving attention, this time from England. Bailey and Shields[94] gave three treatments, at intervals of one week, to 242 hay fever patients. They claimed that no complications occurred, and the results were as follows: complete relief 57.6 per cent, considerable relief 36 per cent, and little or no relief 6.4 per cent. The only comment we can make at the present time is that no results of that type are being obtained in America.

The use of amino-acetic acid (glycine) in asthma suggested itself to Beard and Thiberge[95] from the results obtained with the hydrolytic

products of proteins. Doses of 10 to 20 gm. of glycine dissolved in water were given daily. In a series of 10 patients with asthma or other allergy, improvement was noted in the majority.

Of 25 cases of bronchial asthma treated by McEachern[96] with x-ray, 84 per cent showed improvement. Six were completely relieved, 7 had 75 to 95 per cent improvement, 8 had slight to 50 per cent improvement, and 4 were unimproved or made worse. Typical reactions developed in 21, occurring on the third or fourth day and consisting of marked increase and thinning of sputum and usually an aggravation of the asthma. These symptoms abated after a day or two. The author believes that the good results obtained are probably due to the thinning of the sputum and subsequent probable glandular fibrosis. The technique used was: KV 180; MA 8; 50 cm.; 0.25 mm. Cu., and 1 mm. Al. The posterior aspect of the mediastinum is divided into upper and lower ports of 15 × 15 cm. Each port receives 500 R units in doses of 100 R units a day to alternate ports. The treatments cover a period of ten days. The patient receives about ⅔ of a skin erythema during this time.

Baar[97] combines irradiation of the spleen with cutaneous tuberculin treatment, for which combination he claims cures in 6 cases.

Maytum and Leddy[98] describe the results of x-ray therapy in 23 cases of asthma. In 5 (21.8 per cent) they obtained marked and lasting relief; in 8 (35 per cent) they obtained 50 to 75 per cent relief lasting from three weeks to two months, and in 10 (43.5 per cent) the result was a failure. They have used several techniques but they favor irradiation of the thorax through two paravertebral fields, using the following factors: KV 135; MA 5; 40 cm. distance; 6 mm. Al.; time twenty-two to twenty-six minutes.

Intraperitoneal injections of 250 to 300 c.c. oxygen, usually every three or four days, were found to be helpful by Sisti[99] in four cases of asthma, one of whom had marked emphysema. The possibility of this form of treatment suggested itself to the author from the results obtained in the asthma in a patient who was afflicted with the latter but who was under treatment for intestinal tuberculosis with pneumoperitoneum.

Five cases of asthma treated by transcerebrospinal calcium iontophoresis are reported by Barnett.[100] The method consists in placing a block tin electrode, 1 cm. square, covered with absorbent cotton soaked in 1 per cent calcium chloride to one eye while a second electrode, of 10 sq. cm. area, covered with cotton soaked in tap water is applied to the lumbar spine. A current of 4 to 6 MA. is then passed through for thirty minutes. The treatments are given daily at first until relief begins, then gradually the intervals are lengthened. The author obtained permanent relief in three cases and temporary relief in two cases of long standing asthma showing pulmonary changes.

Attention has already been called to several articles dealing with the psychic factors in asthma. Strauss[6] is of the opinion that in many instances psychotherapy is of great help. The latter may take the form of a psychoanalysis, personality analysis, modification of the environment of the sufferer, and simple suggestion. Clarkson[7] seems to stress the use of hypnosis and suggestion. Galup[101] believes that emotion, suggestion, and psychic association play prominent rôles in the production of asthma. Asthma of psychic origin is compared by him to the occurrence of conditioned reflexes. He believes that by studying these conditioned reflexes one may find a way of helping these patients. Without going further into this phase of the subject at this time, it is quite evident that what is needed is a close, cooperative, sane, and unbiased study carried on jointly by psychiatrists and asthma specialists.

As one reviews the literature of asthma and hay fever year after year it is apparent that there is a constant progression in the addition to our knowledge of the causes, diagnosis, and treatment of these conditions. Radical progress is still awaiting. A cure-all has not yet been found. Perhaps some genius not yet on the horizon will make this possible. At present, however, it is the reviewer's feeling that progress in allergy would be more assured and positive if concerted efforts were made in research, utilizing the knowledge and skill of specialists in various clinical phases and the sciences. To this end a greater interest in allergy will have to be cultivated on the part of research institutions and universities. The good arising from successful research efforts in allergy can benefit many millions of people. It is a goal well worth while.

REFERENCES

1. Asthma Research Council: Report of Progress for the Year Ended 31st October, 1937.
2. Cohen, M. B., and Friedmar, S.: Scorings in the Long Bones as a Guide in the Management of Food Allergy in Children, J. ALLERGY **9**: 54, 1937.
3. Chobot, R., and Merrill, E. F.: Bone Scorings in Normal and Allergic Children, J. ALLERGY **8**: 588, 1937.
4. Debré, R., Lamy, M., and Bernard, J.: Medullary Eosinophilia of Asthmatics, Compt. rend. Soc. de biol. **123**: 679, 1937.
5. Sangiorgi, P.: Significance of Constitutional Factors in Allergic Bronchial Asthma, Rassegna internaz di clin. e terap. **18**: 357, 1937.
6. Strauss, E. B.: The Psychogenic Factor in Asthma, Guy's Hosp. Rep. **87**: 273, 1937.
7. Clarkson, A. K.: The Nervous Factor in Juvenile Asthma, Brit. M. J. **2**: 845, 1937.
8. Rogerson, C. H.: The Psychological Factors in Asthma-Prurigo, Quart. J. Med. **6**: 367, 1937.
9. Piness, G., Miller, H., and Sullivan, E. B.: The Intelligence Rating of the Allergic Child, J. ALLERGY **8**: 168, 1937.
10. Lamson, R. W., and Butt, E. M.: "Fatal Asthma," a Clinical and Pathologic Consideration of 187 Cases, J. A. M. A. **108**: 1843, 1937.
11. Wiseman, J. R.: Report of a Case of Status Asthmaticus with Autopsy, Ann. Int. Med. **11**: 212, 1937.

12. Fowler, K.: Necropsy Studies on Two Patients Dying in Asthma, Pennsylvania M. J. **40**: 720, 1937.
13. Dahl, B.: Death Due to Pollen Injection in the Treatment of Hay Asthma, Klin. Wchnschr. **16**: 491, 1937.
14. Faulkner, W. B., Jr., and Wagner, R. J.: Fatal Spontaneous Pneumothorax and Subcutaneous Emphysema in an Asthmatic, J. ALLERGY **8**: 267, 1937.
15. Kibler, C. S., and Watson, S. H.: Pulmonary Emphysema, Dis. of Chest **2**: 8, 1936.
16. Moll, H. H.: Chest Deformities in Asthma, Lancet **1**: 12, 1937.
17. Colton, W. A., and Ziskin, T.: The Heart in Bronchial Asthma, J. ALLERGY **8**: 347, 1937.
18. Anthony, A. J.: Heart and Circulation in Emphysema and Bronchial Asthma, Verhandl. d. deutsch. Gesellsch. f. Kreislaufforsch. 201, 1937.
19. Kallös, P., and Pagel, W.: Experimental Studies in Bronchial Asthma, Acta med. Scandinav. **91**: 292, 1937.
20. Bernstein, C., Jr., and Ginsberg, J. E.: Sensitization to Milk as a Result of Its Use in Non-specific Foreign Protein Therapy, J. A. M. A. **108**: 193, 1937.
21. van Niekerk, G. J.: Anaphylaxis and Vitamin C, J. ALLERGY **8**: 446, 1937.
22. Boros, E.: Hay Fever and Asthma During and After Jaundice, J. A. M. A. **109**: 113, 1937.
23. Feinberg, S. M., and Bernstein, T. B.: A Method of Measuring Rate and Degree of Absorption of Antigens, J. ALLERGY **8**: 523, 1937.
24. Cowie, D. M.: Auto Passive Transfer in Allergy, Ann. Int. Med. **11**: 949, 1937.
25. Stull, A., Sherman, W. B., and Cooke, R. A.: The Association with Pseudoglobulin of the Skin Sensitizing Substance of Allergic (Hay Fever) Serum, J. ALLERGY **9**: 7, 1937.
26. Waldbott, G. L., and Ascher, M. S.: Skin Reactivity in Cases of Asthma of Short Duration, J. ALLERGY **8**: 246, 1937.
27. Harley, D.: Hay Fever. (I) The Effect of Pollen Therapy on the Skin Reactions. (II) A Reaction-Inhibiting Substance in the Serum of Treated Patients, J. Path. & Bact. **44**: 589, 1937.
28. Baldwin, L. B., and Glaser, J.: Effect of Treatment on Skin and Mucous Membrane Sensitivity and on Reagins in Hay Fever, J. ALLERGY **8**: 129, 1937.
29. Haworth, E., and MacDonald, A. D.: On Histamine in Cotton Dust and in the Blood of Cotton Workers, J. Hyg. **37**: 234, 1937.
30. Bullen, S. S., and Bloor, W. R.: Lipids of the Blood Plasma in Hay Fever and Asthma, J. ALLERGY **8**: 155, 1937.
31. Wagner, H. C., and Rackemann, F. M.: Triplicate Determinations of the Sugar Tolerance in Mild and Severe Asthma, J. ALLERGY **8**: 353, 1937.
32. Black, J. H., and Kemp, H. A.: Blood Density in Guinea Pig Anaphylaxis and in Hay Fever Artificially Induced, Am. J. Clin. Path. **7**: 300, 1937.
33. Grant, L. R.: A Brief Study of Corn Cockle as an Allergen, J. ALLERGY **8**: 506, 1937.
34. Weston, C. G.: Derris Root—A New Allergen, J. ALLERGY **9**: 62, 1937.
35. Chiorazzo, G.: Asthma From Silk Shreds, Riforma med. **53**: 805, 1937.
36. Swineford, O., Jr.: Hypersensitiveness to "Asthma Powders," J. ALLERGY **8**: 607, 1937.
37. Prickman, L. E., and Buchstein, H. F.: Hypersensitivity to Acetyl Salicylic Acid (Aspirin), J. A. M. A. **108**: 445, 1937.
38. Criep, L. H.: Allergy to Dyes, J. A. M. A. **108**: 1169, 1937.
39. Wittich, F. W., and Stakman, E. C.: Case of Respiratory Allergy Due to Inhalation of Grain Smuts, J. ALLERGY **8**: 189, 1937.
40. Bernton, H. S., and Thom, C.: The Rôle of Cladosporium, a Common Mold in Allergy, J. ALLERGY **8**: 363, 1937.
41. Prince, H. E., and Morrow, M. B.: Molds in the Etiology of Asthma and Hay Fever with Special Reference to the Coastal Areas of Texas, South. M. J. **30**: 754, 1937.
42. Feinberg, S. M.: Asthma and Allergic Rhinitis from Molds, Journal-Lancet **57**: 87, 1937.
43. Wagner, H. C., and Rackemann, F. M.: Kapok and Molds: An Important Combination, Ann. Int. Med. **11**: 505, 1937.

44. Tuft, L., and Blumstein, G.: Incidence and Importance of Tree Pollen Hay Fever with Particular Reference to Philadelphia and Vicinity, J. ALLERGY **8**: 464, 1937.
45. Blumstein, G., and Tuft, L.: Plantain Hay Fever, J. A. M. A. **108**: 1500, 1937.
46. McMinn, H. E., and Graham, B. A.: Another Plant Causing Hay Fever in California, J. ALLERGY **8**: 194, 1937.
47. Langley, W. D.: Sensitivity to Piqueria Pollen with Case Report, J. ALLERGY **9**: 60, 1937.
48. Zoss, A. R., Koch, C. A., and Hirose, R. S.: Alum-Ragweed Precipitate: Preparation and Clinical Investigation, Preliminary Report, J. ALLERGY **8**: 329, 1937.
49. Service, W. C.: Antigenic Studies of Polysaccharides Isolated from Pollen, Colorado Med. **34**: 468, 1937.
50. Gelfand, H. H., Flamm, G., Center, J. G., and Heifitz, A. J.: Studies in the Preparation of Pollen Extracts; I. Filtration by Carbon Dioxide Pressure, J. ALLERGY **8**: 336, 1937.
51. Cocke, E. C.: Calculating Pollen Concentration of the Air, J. ALLERGY **8**: 601, 1937.
52. Farmer, L.: On the Immunologic Relationship Between Grass Pollen and Seed, J. ALLERGY **8**: 338, 1937.
53. Berkoff, H. S.: Non-Pollen Inhalants in Hay Fever; a Study of Their Part in Its Symptomatology, New York State J. Med. **37**: 1499, 1937.
54. Rynes, S. E.: A Critical Analysis of Animal Dander Reactions, J. ALLERGY **8**: 470, 1937.
55. Wagner, H. C., and Rackemann, F. M.: Crossed Reactions to Household Dust, J. ALLERGY **8**: 537, 1937.
56. Pipes, D.: The Incidence of Major and Minor Allergy in the Deep South, South. M. J. **30**: 1012, 1937.
57. Withers, O. R.: Food Allergens. A Statistical Study of Forty-Three Cases Relative to the Genetic Classification of Foods, South. M. J. **30**: 918, 1937.
58. Rinkel, H. J.: Respiratory Allergy; Diagnosis and Treatment, J. Missouri M. A. **34**: 327, 1937.
59. Parlato, S. J.: Deficiency of Atmospheric Humidity as a Contributing Factor in Prolonged Asthma, J. ALLERGY **8**: 566, 1937.
60. Weil, C. K.: Hay Fever in Alabama. I. The Flora of Alabama, and II, Analysis of 100 Cases, J. M. A. Alabama **6**: 302 and 329, 1937.
61. Schonwald, P.: Atmospheric Causes of Allergy in Western Washington, Northwest. Med. **36**: 14, 1937.
62. Durham, O. C.: Evaluation of the Ragweed Hay Fever Resort Areas of North America, J. ALLERGY **8**: 175, 1937.
63. Jamieson, H. S.: Hay Fever in Alberta, Canad. M. A. J. **36**: 595, 1937.
64. Gonzalez, M., and Lombardo, A.: Asthmagenic Flora of Uruguay, An. de oto-rino-laring. d. Uruguay **7**: 32, 1937.
65. Bozzola, J. A.: Contribution to the Study of Allergic Flora of Argentina, Semana méd. **24**: 1359, 1937.
66. Bouzat, L. G.: Contribution to the Study of Hay Fever in the City of Bahia Blanca, Presna méd. argent. **24**: 1359, 1937.
67. Sharwood, M. M.: Further Studies of the Pollen Content of the Melbourne Air, M. J. Australia **1**: 4, 1937.
68. Durham, O. C.: Incidence of Air-Borne Fungus Spores, J. ALLERGY **8**: 480, 1937.
69. Pearson, R. S. B.: Observations on Skin Reactivity in Asthmatic and Control Subjects, Quart. J. Med. **6**: 165, 1937.
70. Clarke, J. A., Jr.: Accurate Diagnosis of Hay Fever, Pennsylvania M. J. **40**: 498, 1937.
71. Swineford, O., Jr., and Grove, P. T.: Effects of Adrenalin on Skin Reactions, J. ALLERGY **8**: 475, 1937.
72. Blumstein, G. I.: The Dry Pollen Nasal Test, J. ALLERGY **8**: 321, 1937.
73. Squier, T. L., and Madison, F. W.: The Hematologic Response in Food Allergy. Eosinophilia in the Leucopenic Index, J. ALLERGY **8**: 250, 1937.
74. Otto, E.: Significance of Expiration Pressure in the Clinic, Particularly in Asthmatic Individuals; a Method of Measurement, München. med. Wchnschr. **84**: 738, 1937.

75. Swineford, O. Jr., and Magruder, R. G.: Asthma in Heart Disease; A Clinical Study with Especial Reference to Cardiac Asthma, South. M. J. **30**: 829, 1937.
76. Spain, W. C., and Fuchs, A. M.: A Clinical Study of the Advantages of the Perennial Treatment of Hay Fever, South. M. J. **30**: 1199, 1937.
77. Waldbott, G. L., and Ascher, M. S.: Further Observation on Rapid Hyposensitization, Ann. Int. Med. **10**: 1556, 1937.
78. Waldbott, G. L., and Ascher, M. S.: The Optimal Dose in Pollen Therapy, J. ALLERGY **8**: 457, 1937.
79. Clarke, J. A., Jr., and Leopold, H. C.: Prophylactic Treatment for Ragweed Hay Fever, J. ALLERGY **8**: 560, 1937.
80. Furstenberg, F. F., and Gay, L. N.: The Occurrence of Constitutional Reactions in the Treatment of Hay Fever and Asthma: Analysis of the Causative Factors, Bull. Johns Hopkins Hosp. **60**: 412, 1937.
81. Stier, R. F. E., and Hollister, G.: Desensitization by Oral Administration of Pollen Extracts, Northwest. Med. **36**: 166, 1937.
82. McGrew, G. D.: Time and Money Saved in the Treatment of Hay Fever, Mil. Surgeon **80**: 371, 1937.
83. Urbach, E.: Biological Management of Hay Fever, München. med. Wchnschr. **84**: 488, 1937.
83a. Bernstein, T. B., and Feinberg, S. M.: Oral Ragweed Pollen Therapy. Experiments in Gastrointestinal Absorption and Clinical Results. To be published in Arch. Int. Med.
84. Bernstein, C., Jr., and Kirsner, J. B.: Oral Pollen Therapy; Experimental Considerations, J. ALLERGY **8**: 221, 1937.
85. Herrmann, G., and Aynesworth, M. B.: Successful Treatment of Persistent Extreme Dyspnea, "Status Asthmaticus." Use of Theophylline Ethylene Diamine (Aminophylline, U. S. P.) Intravenously, J. Lab. & Clin. Med. **23**: 135, 1937.
86. Greene, J. A., Paul, W. D., and Feller, A. E.: The Action of Theophylline with Ethylenediamine; On Intrathecal and Venous Pressures in Cardiac Failure and in Bronchial Asthma, J. A. M. A. **109**: 1712, 1937.
87. Black, J. H.: The Control of Allergic Manifestations by Phenyl-Propanol-Amine (Propadrin) Hydrochloride, Journal-Lancet **57**: 101, 1937.
88. Kahn, I. S.: Status Asthmaticus, J. ALLERGY **8**: 158, 1937.
89. Kahn, I. S.: The Relief of Chronic Intractable Bronchial Asthma by Intentionally Induced Ether Anesthesia, South. M. J. **30**: 609, 1937.
90. Fuchs, A. M.: The Interruption of the Asthmatic Crisis by Tribromethane (Avertin), J. ALLERGY **8**: 340, 1937.
91. Carl, A. V.: The Use of Adrenal Cortex in Asthma, M. Rec. **145**: 29, 1937.
92. Criep, L. H., and Hampsey, J. W.: Therapeutic Value of Iodized Oil in Bronchial Asthma, J. ALLERGY **9**: 23, 1937.
93. Libman, J., and Bigland, A. D.: Autogenous Urinary Proteose in Asthma and Other Allergic Conditions, Brit. M. J. **1**: 65, 1937.
94. Bailey, L. D., and Shields, C.: Treatment of Hay Fever by Intranasal Zinc Ionization; Preliminary Report of 243 Cases, Brit. M. J. **1**: 808, 1937.
95. Beard, H. H., and Thiberge, N. T.: The Treatment of Allergic Conditions with Amino-Acetic Acid, M. Rec. **145**: 254, 1937.
96. McEachern, J. M.: X-Ray Therapy in Bronchial Asthma, Canad. M. A. J. **37**: 573, 1937.
97. Baar, V.: Concerning Six Cured Cases of Asthma; Cutaneous Applications of "Dermotubin" Combined with Roentgen Irradiation of Hilum, Wien. med. Wchnschr. **87**: 790, 1937.
98. Maytum, C. K., and Leddy, E. T.: Roentgen Therapy for Severe Asthma, Texas State J. Med. **32**: 610, 1937.
99. Sisti, M. A.: Pneumoperitoneum in the Treatment of Bronchial Asthma, Policlinico **43**: 2049, 1936.
100. Barnett, A.: Transcerebro-Spinal Calcium Iontophoresis in Bronchial Asthma (Preliminary Report), Arch. Phys. Therapy **18**: 646, 1937.
101. Galup, P.: Asthma of Psychic Origin, Gaz. méd. de France **44**: 403, 1937.

185 NORTH WABASH AVENUE

Selected Abstracts

Asthma and Hay Fever

UNDER THE DIRECTION OF SAMUEL M. FEINBERG, M.D., CHICAGO

Experimental Studies of Bronchial Asthma. Kallös, P., and Pagel, W.: Acta med. Scandinav. **91**: 292, 1937.

In sensitized guinea pigs, the inhalation of the antigen produced attacks which corresponded to human bronchial asthma clinically, roentgenologically, immunobiologically, and in reaction to drugs. Inhalation of a fine spray of histamine or acetylcholine solution produced clinical symptoms in guinea pigs corresponding to allergic asthma.

In the shocked allergic animals, histologic examination revealed characteristic findings, especially an eosinophile reaction in the walls of the medium-sized bronchi up to the formation of eosinophile granulations and other severe changes in the bronchial wall. The histologic changes appear to correspond in smallest detail to that seen in human bronchial asthma.

These local tissue changes were not present in the animals inhaling histamine or acetylcholine. The authors conclude, therefore, that these bodies cannot have any determining significance in the development of the tissue reaction typical of bronchial asthma.

Medullary Eosinophilia of Asthmatics. Debré, R., Lamy, M., and Bernard, J.: Compt. rend. Soc. de biol. **123**: 679, 1937.

Bone marrow studies in young asthmatic children have shown marked increase in eosinophiles, which is especially marked during asthmatic attacks. The bone marrow of the normal infant contains 1 to 4 per cent of eosinophiles, that of the asthmatic youngster usually 10 to 20 per cent. Between attacks this medullary eosinophilia persists but is not as marked. This has been a constant finding in all asthmatics thus far. The eosinophiles are the same type as seen in normal marrow.

Significance of Expiration Pressure in the Clinic, Particularly in Asthma. Otto, E.: München. med. Wchnschr. **84**: 728, 1937.

The author believes that the force of the expiration (Atemstoss) is of significance in asthma. He cites Volhard (München. med. Wchnschr. 928, 1921) as having mentioned it previously and having measured it by the sensation of the stream of air on the palm of the hand held in front of the mouth of the patient. Otto constructed an instrument which definitely registers this pressure. The apparatus consists essentially of a funnel into which the patient expires and which allows the force of the air to be transmitted to a pen registering this pressure in terms of degrees of a circle. In normal healthy men this pressure averaged 115° (91 to 135), in healthy women 91° (69 to 109). After moderate exercise the pressure rose.

A study of 22 asthmatic patients was made. During the attack or in heavy attacks in seven patients the values were below 10°. The following averages were obtained in the 22 patients: in 11 it was under 18°; in 9 it was 27° to 65°; and in two it was 74° to 81°. The determinations could be used as an indication of the progress of the patient and the value of the management. He cites the

resultant increase in the "Atemstoss" when patients were placed in a low pressure chamber (equivalent to altitude of 5000 meters). He also was able to show the effects of medication of various types. Breathing exercises were found to raise the pressure from 15° to 30°. Similar lowering of pressure was obtained in emphysema, but in other respiratory diseases the results were less marked.

Asthma Research Council. Report of Progress for the Year Ending October 31, 1937.

At Guy's Hospital, 531 new patients were treated during the year, with a total of 4,349 attendances. Among other projects, some interesting observations have been made on the sedimentation rate which indicate that an approaching attack of asthma may be anticipated by a rising rate.

At St. Mary's Hospital, 946 new patients were seen with 15,236 attandances, in spite of the fact that many were entrusted to home treatment by themselves or their private physicians. Some work has been going on which indicates a common antigenicity of all grass pollens, even of the exotic plants. They found that even such foreign pollen as that of bamboo or sugar cane will react in grass-sensitive patients and desensitize them.

The main project at King's College Hospital is remedial breathing exercises. The results obtained by the latter in asthma cases are reported to be as follows: 40 per cent entirely or almost entirely relieved, 30 per cent very much improved, and 30 per cent either not improved or not cooperating in treatment.

At King's College, studies are also being pursued on spontaneous and induced variability in specific hypersensitivity. The effect of various chemical compounds on the isolated lungs of sensitized animals is another investigation being conducted.

Dr. D'Silva of St. Bartholomew's Hospital Medical College appears to have developed a method making possible adrenalin estimations in protein media. With this aid they intend to make studies on the blood of asthmatics relative to the question of the probable presence of adrenalin deficiency.

Pneumoperitoneum in the Treatment of Bronchial Asthma. Sisti, M. A.: Policlinico **43**: 2099, 1936.

Sisti reports four patients with bronchial asthma, of whom one had marked emphysema, who obtained marked improvement from intraperitoneal injections of oxygen. The latter were given in amounts of 250 to 300 c.c., usually every three or four days. The author's attention to possibilities in this form of treatment was directed by the effect on the asthma in a patient who was afflicted with the latter but who was under treatment for intestinal tuberculosis with pneumoperitoneum.

Dermatology

UNDER THE DIRECTION OF MARION B. SULZBERGER, M.D., NEW YORK CITY, AND JOSEPH GOODMAN, M.D., BOSTON

Studies on the Sensitization of Animals with Simple Chemical Compounds. IV. Anaphylaxis Induced by Picryl Chloride and 2:4 Dinitrochlorobenzene. Landsteiner, K., and Chase, M. W.: J. Exper. Med. **66**: 337, 1937.

The authors injected intracutaneously into guinea pigs small amounts of one or the other of the chemicals named in the title, usually giving daily injections for fifteen days. After a rest period of two to three weeks, the animals were re-

injected with small quantities of conjugates of the same chemical with guinea pig or horse serum. It was found that the intravenous injection of 0.2 mg. to 4.0 mg. of the picryl chloride-protein conjugate was sufficient to induce fatal anaphylactic shock in the animals sensitized to picryl chloride. Intravenous injection of the dinitrochlorobenzene-protein conjugate also produced fatal anaphylaxis in the animals sensitized to the unconjugated chemical, but these reactions were variable and fatal reactions were few. Schultz-Dale reactions were also positive in animals sensitized to these chemicals. Desensitization of animals sensitized to picryl chloride could be obtained as far as anaphylaxis was concerned, by means of injecting picryl chloride-guinea pig serum conjugate subcutaneously prior to the intravenous shocking injection. However, such desensitization had no effect on the reactivity of the skin of sensitized guinea pigs to the surface application of unconjugated picryl chloride.

It was found that skin sensitivity to the surface application of the simple chemical could not be induced by intradermal injection of the protein conjugate, even though such injections were successful in inducing anaphylactic hypersensitivity. Also the skin could not be passively sensitized to the simple substances by application to the skin of serums containing anaphylactic antibodies to these substances.

However, in view of the fact that the anaphylactic state is induced by the same injections which give rise to the hypersensitivity of the skin and in view of the fact that the substances here producing the anaphylactic sensitivity are known to cause contact-type skin sensitivity in man, the authors feel that there is justification for the assumption that the formation of conjugated antigens offers an explanation for the skin effects also. They feel that support for this hypothesis is found especially in the chemical characteristics of the substances employed, each of which forms conjugates very easily. Antibodies in the broadest sense of the word must then be assumed a priori for contact dermatitis, although they have not as yet been experimentally established.

Studies of an Urticarial Response to Blue and Violet Light in Man. Blum, H. F., and West, R. J.: J. Clin. Investigation **16**: 261, 1937.

The authors performed careful studies of the light sensitivity of a patient with *urticaria solare*. The urticarial response was produced in this individual only by light of the visible spectrum between 3900 and 5300 Å and was not produced by ultraviolet light. The response obeyed the reciprocity law. Studies of the effect of temperature indicated that the mechanism of the response included a photochemical reaction which was not greatly affected by temperature and a thermal reaction which was greatly modified by changes in temperature. The exposed parts of the patient were less sensitive than parts covered by clothing. In the course of ten months, there was very little change in the degree of sensitivity. Studies with filters which transmitted only narrow spectral bands demonstrated that there were two regions of maximum sensitivity. In general, the curve corresponded to the absorption curves of the carotenoid pigments, although it could not be demonstrated that a carotenoid pigment was responsible for the symptoms in the patient studied.

The patient had no past or family history of allergy. Scratch tests with food, pollen, and epidermal extracts were negative. Passive transference experiments were also negative. The onset of the patient's difficulty was within a few days after a bee sting. Although the patient showed a greater reaction than the normal to a bee venom dilution, desensitization with bee venom was of no avail.

The authors concluded that allergy in the usual sense of the word is not a factor in the condition studied, and that it is probable that a carotenoid pigment is the photosensitizer responsible for the production of this condition.

The Production of the Shwartzman Phenomenon by Means of Bacterial Extracts. Antopol, W.: J. Infect. Dis. **61**: 331, 1937.

After repeated extraction of *B. Typhosus* with 95 per cent alcohol and with the normal saline, the author recovered from the pooled extraction fluids a substance which, in doses of 20 mg. intradermally followed in twelve to twenty-four hours by a like amount intravenously, produced typical Shwartzman reactions in the rabbit. Similar results were obtained with colon bacillus, *pneumococcus* Type III, *meningococcus, B. dysenteriae,* and *B. Proteus.* All of these extracts could be used interchangeably with the original Shwartzman filtrate.

It was found that an intravenous injection of 0.0005 mg. of the *B. Proteus* extract resulted in a positive skin reaction if the skin preparatory dose was 0.5 mg. or more. With a larger intravenous dose, a smaller intradermal dose was capable of preparing the skin site.

The Use of Tumor Extracts in the Production of the Shwartzman Phenomenon. Antopol, W.: J. Infect. Dis. **61**: 334, 1937.

The author found that without previous skin preparation the bacterial extracts described in the previous communication were capable of producing hemorrhagic reactions in the transplanted tumor of Sarcoma 180 in mice. Therefore, an attempt was made to find evidence for the existence of the skin preparatory factor in human tumors. Nine human tumors were studied, including 5 carcinomas of the breast. Six of the nine were shown to contain a skin preparatory factor. Cultures from the tumors, before preparation of the extracts, were negative in four of these six cases. In one instance, the tumor extract was found to produce a typical Shwartzman phenomenon in skin prepared by the previously described *B. Proteus* extract. Sarcoma 180 in mice was also found to contain a skin preparatory factor.

Schultz-Dale Experiments with Tuberculin Preparations. Jadassohn, W., Reidmuller, L., Schaaf, F., and Zurcher, W.: Schweiz. med. Wchnschr. **67**: 77, 1937.

The authors demonstrated by Schultz-Dale experiments that human and avian old tuberculins contain one or more common antigens but no antigen peculiar to either old tuberculin; and that an extract of bacillus *phlei* (a nonpathogenic acid-fast organism) contains no antigen found in old tuberculin but does contain an antigen not present in old tuberculin. Similar experiments with human Ertuban (an aqueous extract from washed tubercle bacillus bodies) demonstrated that human Ertuban contains no antigen found in human old tuberculin but does contain an antigen not found in human old tuberculin. Further Schultz-Dale experiments demonstrated that there was a common antigen in one human and in one bovine Ertuban, that one bovine Ertuban contained an antigen that was absent from two human Ertubans, and that the same two human Ertubans contained an antigen that was absent from the bovine Ertuban.

Seasonal Cycle of Allergy to Tuberculin. Rigoni, M.., and Zanfrognini, G.: Minerva med. **28**: 161, 1937.

The authors performed the Mantoux test on 1,630 patients over a period of five years. It was demonstrated by plotting the results that the intensity of the reaction to tuberculin presented two peaks during the year, the higher one occurring between March and May and the lower in October and November. These peaks occurred with regularity during each year studied.

Theoretical questions raised by this finding are discussed by the authors.

Tuberculin Skin Sensitivity in Chronic Tuberculosis in Course of Hospital Treatment: Measurement by Standard Tuberculin (Purified Protein Derivative). Hayes, M. G., Pastor, J. R., Gaetan, L. R., Cory, R. A. S., and Long, E. R.: Am. J. M. Sc. **194**: 220, 1937.

The authors performed monthly skin tests on 116 patients with chronic pulmonary tuberculosis, 20 of whom were under observation for about one year and 67 of whom were under observation for more than four months. Purified protein derivative in doses of 0.00002 mg. and 0.005 mg. was used for all tests. The general level of sensitiveness to tuberculin was low. Strong reactions were not found. More than half of the patients followed longer than five months maintained approximately the same level of sensitivity. While it was noted that certain patients with an unfavorable course tended to lose their tuberculin sensitivity, a definite continuing depression of sensitivity was observed also in patients with chronic tuberculosis of long duration but somewhat favorable course. Also transient or prolonged increase in sensitivity occurred in many patients with clinical improvement. No correlation could be established between the tuberculin sensitivity and the patient's temperature or between tuberculin sensitivity and seasonal influences.

Immunology

UNDER THE DIRECTION OF MATHEW WALZER, M.D., BROOKLYN

Chemo-Immunological Studies on Conjugated Carbohydrate-Proteins; Specificity of Azoprotein Antigens Containing Glucuronic and Galacturonic Acids. Goebel, W. F., and Hotchkiss, R. I.: J. Exper. Med. **66**: 191, 1937.

In view of the presence of the uronic acid nucleus, as glucuronic or galacturonic acid, in the capsular polysaccharides of certain types of pneumococci, the authors considered it important to compare the serological properties of artificially compounded antigens containing these compounds.

Rabbits were immunized with antigens prepared by combining diazonium derivatives of p-aminobenzyl beta glycosides of glucose, galactose, glucuronic, and galacturonic acids with normal horse serum. The test antigens consisted of the glycosides combined with the protein of chicken serum in order to avoid protein cross reactions.

Rabbits, immunized with these azoprotein antigens, produced antibodies specific for the antigen use. Precipitin reactions were inhibited only by homologous and not by heterologous glycosides. The writers showed that, although the stereochemical pattern of glucose and glucuronic acid were identical, antigens prepared from these gave rise in rabbits to antibodies with no serologic crossing. The difference in the immunologic properties of these two chemicals, was, therefore, shown to be due to a difference in polarity. Antigens containing stereo-isomeric uronic acids, glucuronic, and galacturonic displayed an individual specificity, indicating that the minimum response of rabbits is directed toward the carbohydrate radical as a whole and not to any individual grouping in particular.

The writers further reported that glucuronic and galacturonic acid antigens precipitate in antipneumococcic horse serums but not in normal horse serum, antipneumococcic rabbit serums or in immune horse serum from which the type-specific antibody has been removed by absorption. The authors are of the opinion that this phenomenon may possibly be attributed to a reaction between the acidic

groups of antigen and the basic groups of the antibody protein molecule. The absence of precipitation in rabbit immune serums denotes a further difference between the immune proteins of rabbit and horse serums.

Anaphylaxis With Tobacco Mosaic Virus Protein and Hemocyanine. Seastone, C. V., Loring, H. S., and Chester, K. S.: J. Immunol. **33**: 407, 1937.

The experiments reported in the present communication represent an attempt on the part of the authors to demonstrate anaphylactic shock in vivo with the high molecular weight protein recently isolated by Stanley from extracts of plants infected with tobacco mosaic virus.

Guinea pigs were sensitized with several times crystallized tobacco mosaic virus protein. Reinjection with the same material, three weeks later, resulted in anaphylactic shock. However, samples of virus protein were found to give crossed reactions to proteins of normal tobacco plants. To eliminate this factor, the authors obtained a preparation of virus protein, purified by ultra-centrifugations, which gave no cross reactions with the proteins of normal tobacco plants. Using this preparation for sensitization and shocking, the authors report fatal anaphylaxis in guinea pigs, even after injection of normal tobacco protein preliminary to administration of the shocking dose. As reported previously by one of the authors, tobacco mosaic virus protein failed to cause smooth muscle contraction in sensitized guinea pigs by the Schultz-Dale technique.

Experiments with the hemocyanine of *Limulus polyphemus,* having a molecular weight of about one-sixth that of tobacco mosaic virus protein, showed this protein to be anaphylactogenic in the Schultz-Dale, as well as in the in vivo method.

In the absence of precipitin demonstration and with negative results with the uterine horn technique, it is difficult to accept the high molecular weight protein of tobacco mosaic virus as truly anaphylactogenic.

The Antigenic Behavior of Serum Proteins With Special Reference to Crystalbumin and Seroglycoid. Hewitt, L. F.: Biochem. J. **31**: 1047, 1937.

The author is of the opinion that considerable difference in experimental methods and wide variation in the purity of the antigens used have contributed to great confusion in the literature concerning the antigenicity of serum proteins, especially the albumin fraction.

Using purified antigens, fractionated from horse serum, to sensitize and shock rabbits and the optimum proportions technique of Dean and Webb for precipitin determination, the author, in the present communication, presents his studies on the antigenic behavior of serum proteins.

The antigenic function of serum albumin was shown to be due mainly to the presence of seroglycoid and traces of pseudoglobulin. Crystalbumin, which constitutes the bulk of the albumin fraction, proved to be only feebly antigenic.

Blood serum, in the opinion of the writer, consists of at least five specific antigens, which differ in antigenic potency: euglobulin, pseudoglobulin, crystalbumin, seroglycoid, and probably mucoid.

Ascorbic Acid Stimulation of Specific Antibody Production. Madison, R. R., and Manwaring, W. H.: Proc. Soc. Exper. Biol. & Med. **37**: 402, 1937.

The authors report their experiments on the effect of ascorbic acid administration on specific antibody production in rabbits.

Rabbits were sensitized with one intravenous dose of horse serum containing 100 mg. of crystalline synthetic ascorbic acid. A control series received no ascorbic acid. Precipitin titers were followed for a fifty-day period in both series.

Animals receiving ascorbic acid demonstrated a prompter formation of a specific precipitin than the control group. The antibody-stimulating ratio for ascorbic acid was approximately 30:1 during the early stages of immunization, falling to a 12:1 ratio at the height of immunization. While specific precipitins disappeared in the control group at about the fiftieth day, the animals receiving ascorbic acid still showed a residual precipitin titer equal to that of the control group at the height of immunization. The optimal antibody stimulating dose, 37.5 mg. ascorbic acid administered intravenously, resulted in an average fourteen- to twenty-one-day precipitin titer 20 times that of the control group.

Specific antibody stimulation also resulted when horse serum and ascorbic acid were injected intraperitoneally, subcutaneously, or intradermally, or when horse serum and ascorbic acid were injected separately into different depots.

The Immunological Specificity of a Polysaccharide Fraction From Some Common Helminths. Campbell, D. H.: J. Parasitol. **23**: 348, 1937.

In the present paper the author reports his method for the isolation and purification of an antigenic polysaccharide from various helminths, e.g., Ascaris *lumbricoides*, Ascaris *suum*, Parascaris *equorun*, Toxocara *canis*, Cysticercus *fasciolaris*, and Monezia *expansa*. The writer presents experimental data as to the immunologic specificity of these helminths.

Using undried worm material for immunization, rabbit antiserums were prepared against A. *lumbricoides*, A. *suum*, T. *canis*, and M. *expansa*. All serums were tested for nonspecific reactions before use. The polysaccharide antigens were used to test for precipitins by the ring method.

Whereas saline whole worm extracts from all Ascaris forms studied displayed cross reactions with heterologous antiascaris serums, polysaccharide fractions, reacted only with homologous antiserums. These experiments indicated that the specificity of the precipitation reaction is far greater with polysaccharides than with saline extracts of whole worm material, even with the closely allied forms A. *lumbricoides* and A. *suum*.

Pediatrics

UNDER THE DIRECTION OF WILLIAM C. DEAMER, M.D., SAN FRANCISCO

The Psychological Factors in Asthma—Prurigo. Rogerson, C. H.: Quart. J. Med. **6**: 367, 1937.

Following an initial study of 12 children suffering from asthma or "eczema-prurigo" in whom the importance of psychologic factors was evident, a more detailed study was made of 25 unselected cases. The personality-likeness of many of these cases was so striking that "one began to speak very tentatively of an asthma-prurigo personality in which a high intelligence and an underlying aggressiveness were combined with overanxiety and insecurity." There was also an environment-likeness in that the parents were often overprotective and overanxious. The author points out that the personality features are not entirely secondary to either the environment or the illness, but appear to fit in as part of—possibly the chief part of—the allergic constitution.

The individual attack of asthma depends ultimately on a state of tension which the personality and environment favor. The actual precipitating cause over and above this basic factor may be either physical or psychologic—an allergic or

a fright for example. If the tension is removed, the patient may withstand such stimuli without developing an attack. The conclusion which is emphasized is that psychologic treatment is in some cases able to prevent attacks completely, and in many others it is able to assist materially the known physical remedies.

Roentgen Studies of Children With Alimentary Disturbance Due to Food Allergy. Fries, J. H., and Zizmor, J.: Am. J. Dis. Child. **54**: 1239, 1937.

This is a study of twelve children known to have gastrointestinal symptoms due to food allergy. Barium meals containing the offending allergens were given and subsequent x-ray and fluoroscopic studies were compared with those following an ordinary barium meal. Like comparisons were made by means of barium enemas. The disturbances visualized consisted in alterations in tone and motility as shown especially by spasm of the colon and hypomotility and delayed emptying of the stomach. The meal containing the allergen was occasionally followed by spasm of the colon which was not reproduced when an enema containing the same allergen was given. Subjective complaints referable to the gastrointestinal tract usually accompanied objective findings. One generalized reaction occurred following an enema containing nuts which was given to a nut-sensitive patient. The suggestion is made that these procedures may eventually offer an additional diagnostic method.

An Early Sign of Latent Allergy in Infants. Kugelmass, I. N.: Arch. Dermat. & Syph. **36**: 342, 1937.

Pointing out the difficulty of recognizing the potentially allergic child prior to the development of symptoms, Kugelmass states that if retro-auricular intertrigo is present it is pathognomonic of latent allergy. In 80 per cent of infants who showed this condition, he could demonstrate the allergy while the child was under his care. The etiologic agent of the intertrigo is a nonhemolytic streptococcus. The lesion may be glazed, crusted, or fissured and is usually more pronounced on the left side than it is on the right side.

Exogenous Lichen Urticatus. Hamburger, F., and Dietrich, A.: Med. Klin. **34**: 4, 1938.

The importance of insect bites as a cause of lichen *urticatus* in infants and young children is pointed out. This form of chronic urticaria has generally been considered alimentary in origin. However, the authors had previously failed to produce the typical lesions by feeding offending foods, although Urbach stated he had done so. In 17 of 24 cases of lichen *urticatus*, they did succeed in producing a characteristic flare-up by means of insect bites. Fleas and bedbugs were frequently the offenders.

Reactions to "Tuberculin" From an Unusual Type of Acid-Fast Bacillus. Beaven, P. W.: J. Infect. Dis. **62**: 92, 1938.

Eight years ago an acid-fast bacillus designated as the Ryan *Mycobacterium* was isolated from the pleural fluid of an eleven-week-old infant. At the time, the infant had signs resembling lobar pneumonia and today still shows marked changes, by x-ray, which in many respects resemble pulmonary tuberculosis. Five hundred and twenty-five children were tested with ordinary human tuberculin and with Ryan "tuberculin," prepared from organisms originating in this case. Twenty-six reacted exclusively to Ryan "tuberculin." Five of the 26 had pulmonary lesions

somewhat analogous to those noted in the child infected with the Ryan bacillus. In none was it possible to demonstrate the organism itself. Fifty-three children in the group reacted to both human and Ryan tuberculin. It is suggested that a certain number of children in the general population are infected with the Ryan organism.

Rhinology and Ophthalmology

UNDER THE DIRECTION OF FRENCH HANSEL, M.D., ST. LOUIS

Further Studies in the Hydrogen Ion Concentration of Nasal Secretion. Buhrmester, C. C.: Arch. Otolaryng. **27**: 83, 1938.

Buhrmester's report represents further studies on the hydrogen ion concentration of nasal secretions in various diseases of the respiratory tract. In all, 350 determinations were made on 125 patients. The conditions presented were as follows: 6 had atrophic rhinitis; 11 had bronchoscopic treatment; 25 had colds; and 83 had nasal allergy complicated or uncomplicated by infection. It was noted that loss of weight is reflected in the nasal secretion by an increase in the hydrogen ion concentration. The secretion during colds is alkaline in the initial stage and the pH decreases to normal as clinical improvement takes place. She finds the initial physiologic response of the nasal mucosa to stimulation is similar regardless of the inciting agent.

Laryngeal Stenosis Following Tetanus Antitoxin. Taquino, G. J.: South. M. J. **31**: 88, 1938.

Taquino reports a case of laryngeal stenosis following the administration of tetanus antitoxin. The patient was a boy, thirteen years of age. The patient had received an injury for which tetanus antitoxin was administered in large doses over a period of about one week. About a month after the last administration of tetanus antitoxin, the patient developed respiratory difficulty which required tracheotomy. Examination of the larynx made about six weeks later showed a marked hyperplasia and thickening of the ventricular bands.

Retinal Detachment Due to Allergy. Prewitt, L. H.: Arch. Ophth. **18**: 73, 1937.

Prewitt reports a case of retinal detachment probably of allergic origin. The patient, a man aged sixty-two years, gave a past history of urticaria and angioneurotic edema. Previous to complete retinal detachment, several attacks of transient blindness occurred which were usually associated with generalized angioneurotic edema and urticaria. On one occasion following the ingestion of turkey liver, he developed a marked edema of the jaws and cheeks accompanied by large blebs on the cornea of the left eye.

Food Allergy as a Cause of Vasomotor Rhinitis. Eyermann, Chas. H.: South. M. J. **31**: 210, 1938.

Eyermann reports his observations on a group of 181 patients in whom the deliberate ingestion of food induced nasal obstruction, coryza, and sneezing. From his observations, he concludes that multiple skin and clinical sensitivity is the rule rather than the exception and that skin sensitivity is not an unerring guide to clinical sensitivity. He found that the foods most frequently eaten are the ones most likely to induce attacks of nasal allergy. Frequently, food and inhalant avoidance is sufficient to bring about a satisfactory therapeutic result. He emphasizes that in patients with perennial nasal allergy and hay fever, avoidance of food and inhalants other than pollen usually brings about a satisfactory

therapeutic result. He found that when bronchospasm complicates the allergic reaction in the nose, inhalants are more likely to be the dominant causative agents. Before determining that pollen injections are imperative, one should consider the clinical influence of foods and inhalants other than pollen. In many of these cases he feels that the persistence and duration and possibly the initiation and intensity of symptoms depend upon the total allergic dose.

Perennial Allergic Rhinitis: An Analysis of 198 Cases. Winkenwerder, W. L., and Gay, L. N.: Bull. Johns Hopkins Hosp. **61**: 90, 1937.

Winkenwerder and Gay report an analysis of 198 cases of perennial allergic rhinitis encountered in private practice. They found that nasal allergy occurs in all age groups, being most common in young individuals especially before the age of ten years. During the first decade, males predominated but after this period the disease was more frequently encountered in females. It seems rather unusual that only 12 out of 100 patients showed a blood eosinophilia. Approximately 25 per cent of the cases were associated with bronchial asthma; 20 per cent with hay fever; 5 per cent with eczema; and 3 per cent with urticaria. In less than 2 per cent food sensitivity was demonstrated. About 50 per cent of the associated allergic disorders appeared during the first decade. It was stated that dust, feathers, and orris root, singly or in combination, accounted for 95 per cent of the etiologic factors in the cases in this series. Animal danders, kapok, and cottonseed accounted for the remaining 5 per cent. It is noteworthy that the observers failed to find a single case in which food was a causative factor. One hundred and thirty-seven patients were treated by avoidance of the offending factors and by desensitization with specific extracts. In 82 per cent the patients were completely cured or markedly improved; in 18 per cent they remained unimproved. Of 22 cases in this series that showed coexisting infections of the sinuses or tonsils, 11 cleared up following allergic management while 9 required surgical treatment.

Miscellaneous

Sensitivity to Drene Shampoo. Biederman, J. B.: New England J. Med. **217**: 1088, 1937.

Nineteen patients were found who showed allergic manifestations to Drene Shampoo. Ten developed sneezing spells, five asthma, two a combination of the two, one rhinitis and eczema, and one dermatitis. The patients with skin lesions gave positive patch tests. The others gave negative skin tests including intradermal and passive transfer.

Antuitrin-S Intradermal Pregnancy Test. Gill, A. M., and Howkins, J.: Brit. M. J. **2**: 1069, 1937.

Gonadotropic substance from the urine of pregnant women was injected intradermally in 49 men and 98 women of whom 73 were between the fourth and ninth month of pregnancy and 25 were nonpregnant. Of the latter, 15 were in the premenopausal and 10 in the postmenopausal age. Positive reactions were obtained in 44 men, in 51 of the pregnant women, in 13 of the nonpregnant women in the premenopausal age, and in 8 of those in the postmenopausal age. The fallacy of the test was thus revealed. The authors considered the probability that the reaction was due to the presence of a foreign protein. Using material in which the hormone had been inactivated, they further tested 10 men and 31 women with and without pregnancy. Again the test was as fallacious as with the active hormone.

Correspondence

January 6, 1938.

The Editor,
Journal of Allergy.
Dear Sir:

Due to misinterpretations of the significance of bone scorings (which must be distinguished from bone scars or clearly defined transverse lines) apparent in some children near the growing ends of bone particularly on the lower tibia, I am glad to report that neither Dr. Cohen nor I have ever claimed these to be pathognomonic of allergy. We believe them to be due to minor disturbances of metabolism or health mediated through gastrointestinal disturbance, but since the objective signs of disturbance may be equivocal to some minds, we have been willing to speak of the mediating cause as gastrointestinal sensitivity. This may or may not have an allergic origin. Scorings do occur in the gastrointestinal form of allergy and when they are found in this disorder their appearance and disappearance may be used as an indicator of fluctuation in the gastrointestinal expression of the disease. They are analogous to a rise in temperature which is significant of the course of illness but in no way pathognomonic of any particular disease.

In discussing allergy as I was on December 5, 1936, one would naturally refer to these scorings as seen in allergy just as one would discuss temperature in the consideration of pneumonia. That no more justifies an inference that scorings are pathognomonic of allergy than it justifies an inference that rise in temperature is pathognomonic of pneumonia. Perhaps any of your readers who may be in doubt on this subject might refer for further information to my articles in Angle Orthodontist for July, 1937; Proc. Inst. Med. Chicago 11: 234, 1937; or the forthcoming issue of the Am. J. Dis. Child.

Yours sincerely,

(Signed) T. Wingate Todd.